

Anesthesia and Analgesia

Acc.
16.12.87

16

Journal of the International Anesthesia Research Society
Oldest Publication in the Specialty—Established 1922



Organon presents:

The new, distinctive Pavulon[®] vial for positive identification and handling ease.

- New functionally contoured vial speeds selection and helps assure positive identification.
- Easy-grip, no-slip design for better handling.



- Now there is one more reason to choose PAVULON[®], with over 14 years of successful clinical experience.



Pavulon[®]
(pancuronium bromide
injection)

Now...tangibly different.



Anesthesia and Analgesia

Cub - H04023 - 16 - P024586
Journal of the International Anesthesia Research Society
3645 Warrensville Center Road, Cleveland, Ohio 44122 Telephones: (216) 295-1124 or 295-1130

Editorial Board

Editor in Chief

Nicholas M. Greene, MD, New Haven, Connecticut

Editors

David R. Bevan, MA, MB, BChir,
Montreal, Quebec, Canada

D. Ryan Cook, MD, Pittsburgh, Pennsylvania
Benjamin G. Covino, PhD, MD, Boston, Massachusetts
Norig Ellison, MD, Philadelphia, Pennsylvania
Mieczyslaw Finster, MD, New York, New York
Alison B. Froese, MD, Kingston, Ontario, Canada
Edward D. Miller Jr, MD, New York, New York
Walter S. Nimmo, MD, BSc, FRCP, FFARCS,
Sheffield, United Kingdom

Daniel M. Philbin, MD, Boston, Massachusetts
J. Gerald Reves, MD, Durham, North Carolina
Petter A. Steen, MD, Oslo, Norway
John H. Tinker, MD, Iowa City, Iowa
K.C. Wong, MD, PhD, Salt Lake City, Utah

Book Review Editor

Norig Ellison, MD, Philadelphia, Pennsylvania

Editorial correspondence and manuscripts should be addressed to: NICHOLAS M. GREENE, MD, Editor in Chief, *Anesthesia and Analgesia*, Yale University School of Medicine, 333 Cedar Street, New Haven, Connecticut 06510 (Telephone: 203-785-4703). For information concerning preparation of manuscripts see "A Guide for Authors" published quarterly in the Journal. All articles published in this Journal become the property of the International Anesthesia Research Society. Reproduction in whole or part is not permitted except by written consent of the publisher and the author.

Books for review should be sent directly to the Book Review Editor, NORIG ELLISON, MD, Department of Anesthesia, University of Pennsylvania, Philadelphia, Pennsylvania 19104.

Reprints: For single copies, write directly to the senior author at the address listed on the title page. Quantity orders (minimum 100) processed through ELSEVIER SCIENCE PUBLISHING CO, INC, 52 Vanderbilt Avenue, New York, NY 10017, prices on request.

The International Anesthesia Research Society is a nonprofit, scientific, and educational corporation in the state of Ohio. Members of the Board of Trustees of the Society are: Douglas B. Craig, MD, Bruce F. Cullen, MD, E. Paul D. Smith, MD, Judith H. Donegan, MD, PhD, Noel W. Lawson, MD, John T. Morrison, MD, Emerson A. Moffitt, MD, Dean H. Morrow, MD, Robert K. Stoeltz, MD, and John L. Waller, MD. Emeritus Trustees are: Paul R. Dumke, MD, Morris T. Nicholson, MD, B. B. Sankey, MD, and T. H. Seldon, MD.

Anesthesia and Analgesia (ISSN 0003-2999) is issued monthly for the IARS in one indexed volume per year by Elsevier Science Publishing Co, Inc, 52 Vanderbilt Avenue, New York, NY 10017. Printed in USA. © 1985 International Anesthesia Research Society. Second class postage paid at New York, NY and at additional offices.

Subscription information for 1986 applying to IARS members: USA and possessions, \$50.00 per year, in all other countries \$61.00. Membership is available to individuals with doctorate degrees in medicine, osteopathy, dentistry, veterinary medicine, or other disciplines who are engaged in active clinical practice of or research in anesthesiology. ASSOCIATE MEMBERSHIP is available to individuals certified, licensed, or accredited in anesthesia-related professions (CRNA, CRTT, RRT, Physician Assistant). EDUCATIONAL MEMBERSHIP (half the full member price) is available to interns, residents, students in nurse anesthesia and related training programs, for a 2- or 3-year period only upon completion of application including certification by applicant's program director.

All membership payments and correspondence regarding IARS member subscriptions should be sent to: Emerson A. Moffitt, MD, Executive Secretary, International Anesthesia Research Society, 3645 Warrensville Center Road, Cleveland, Ohio 44122.

Subscription information for 1986 applying to non-IARS members: Institutions, \$95.00; nonmember individuals, \$50.00. Outside of the USA and possessions, please add \$11.00 for surface postage and handling. For airmail, add \$40.00 in USA, Canada, and Mexico, \$23.00 for surface airlift to Europe, \$36.00 for surface airlift to Japan, and \$93.00 for airmail to the rest of the world. Postmaster: Send address changes to: *Anesthesia and Analgesia*, Elsevier Science Publishing Co, Inc, 52 Vanderbilt Avenue, New York, NY 10017.

Orders and inquiries regarding institutional and nonmember individual subscriptions should be directed to: Journals Fulfillment, Elsevier Science Publishing Co, Inc, 52 Vanderbilt Avenue, New York, NY 10017. Subscriptions are entered for the calendar year, January-December.

Correspondence inquiries regarding IARS member subscriptions should be sent to the IARS at the Cleveland, Ohio address above. Correspondence regarding all other subscriptions should be sent to Elsevier.

Advertising inquiries should be addressed to: Pharmaceutical Media, Inc, 130 Madison Avenue, New York, NY 10016. The appearance of advertising in publications of the International Anesthesia Research Society does not constitute a guarantee or endorsement of the quality or value of such product or of the claims made for it by its manufacturer. Discussions, views, and recommendations as to medical procedures, choice of drugs, and drug dosages are the responsibility of the authors. Every effort has been made to ensure the accuracy of the information. The editor, publisher, or the Society, however, must disclaim any responsibility or liability. Readers are advised to check package insert information for each drug before administration.

See classified ads section for submission of classified material.

Single issues: Single copy information available from Elsevier Science Publishing Co, Inc, upon request. Back volume (all issues prior to 1983) information available from IARS.



Specify
Quality
of Life...
Simply
& Cost-
Effectively.

Specify CORMED II™ Ambulatory Infusion System

CORMED II Ambulatory Infusion Pump provides therapeutic flexibility & simplicity for you and your patients. CORMED II...no complicated keyboard data entry...no cassettes...no cumbersome multiple connections...and no excess bulk. For you, there's proven pump technology, and freedom to administer precise continuous infusions up to 5 days without battery change. For your patients, there are audible/visual alarms & a constant flow rate display. Plus the convenience & security of an easy-to-use external pump.

CORMED II. A sound response to today's healthcare environment that can measurably improve your patient's quality of life.

- ▲ **Supports wide range of therapies**—6-50ml/day flow range (adjustable in 0.1 ml increments)
- ▲ **Added security**—60CC drug reservoir bag is protected inside pump case (larger volume external bag, optional)
- ▲ **Lower operating costs than disposable batteries**—Rechargeable snap-in 5-day battery
- ▲ **No expensive cassettes or additional tubing sets needed**—Low cost integrated bag & tubing set
- ▲ **Simple to operate**—The only controls are the on-off switch and the rate set knob.

Visit Our CORMED
Exhibit at the **ASA
Meeting in Las Vegas.**

We will be happy to discuss
exactly how you may best utilize
the CORMED II to help control your
patient's pain.



CORMED Inc.™

**World leader in outpatient
ambulatory infusion systems**

591 Mahar Street, Dept. AN8, Medina NY 14103
716-798-4900 • Telex: 501783

Anesthesia and Analgesia

Contents

Volume 65, Number 10, October 1986

SCIENTIFIC ARTICLES

- | | | |
|--|--|------|
| The Influence of Hepatic Plasma Flow on Alfentanil Plasma Concentration Plateaus Achieved with an Infusion Model in Humans: Measurement of Alfentanil Hepatic Extraction Coefficient | <i>M. Chauvin, F. Bonnet, C. Montembault, J. C. Levron, and P. Viars</i> | 999 |
| Effect of Etomidate on the Electroencephalogram of Patients with Epilepsy | <i>Zeyd Y. Ebrahim, Glenn E. DeBoer, Hans Luders, Joseph F. Hahn, and Ronald P. Lesser</i> | 1004 |
| Maternal Cortical Vein Thrombosis and the Obstetric Anesthesiologist | <i>Dirk Younker, Monica M. Jones, Jayshree Adenwala, Alan Citrin, and Thomas H. Joyce III</i> | 1007 |
| Continuous Noninvasive Monitoring of Cardiac Output with Esophageal Doppler Ultrasound during Cardiac Surgery | <i>Jonathan B. Mark, Richard A. Steinbrook, Laverne D. Gugino, Rosemarie Maddi, Barbara Hartwell, Richard Shemin, Verdi DiSesa, and Wasima N. Rida</i> | 1013 |
| Pharmacokinetics and Pharmacodynamics of Alfentanil Infusions during General Anesthesia | <i>Audrey Shafer, Man-Ling Sung, and Paul F. White</i> | 1021 |
| Comparison of Resuscitation of Sheep and Dogs after Bupivacaine-Induced Cardiovascular Collapse | <i>Gregory W. Kasten and Stuart T. Martin</i> | 1029 |
| Epidural Morphine Improves Pain Relief and Maintains Sensory Analgesia during Continuous Epidural Bupivacaine after Abdominal Surgery | <i>N.-C. Hjortso, C. Lund, T. Mogensen, D. Bigler, and H. Kehlet</i> | 1033 |
| Lack of Effect of Intravenous Lidocaine on Hemodynamic Responses to Rapid Sequence Induction of General Anesthesia: A Double-blind Controlled Clinical Trial | <i>Bent Chraemmer-Jørgensen, Poul Flemming Høilund-Carlsen, Jens Marving, and Vinni Christensen</i> | 1037 |
| Spontaneous Recovery of Neuromuscular Function after Atracurium in Pediatric Patients | <i>Olli A. Meretoja and Ilkka Kalli</i> | 1042 |
| Failure of the Tourniquet-Twitch Test as a Diagnostic or Screening Test for Malignant Hyperthermia | <i>Beverley A. Britt, Elizabeth A. Scott, Asia Kleiman, Philip Jones, and David J. Steward</i> | 1047 |

SPECIAL ARTICLE

- | | | |
|---|-------------------------|------|
| Harold Randall Griffith, MD, CM, FRCP(C), FFARCS(ENG), FRCS(C): 1894-1985 | <i>Thomas H. Seldon</i> | 1051 |
|---|-------------------------|------|



REVIEW ARTICLE

- | | | |
|---|----------------------------|------|
| Acquired Immunodeficiency Syndrome: An Overview for Anesthesiologists | <i>Ernest R. Greene Jr</i> | 1054 |
|---|----------------------------|------|

CLINICAL REPORTS

- | | | |
|--|--|------|
| Physostigmine Reversal of General Anesthesia for Intraoperative Neurological Testing: Associated EEG Changes | <i>Alan A. Artru and Geoffrey S. Hui</i> | 1059 |
| Posterior Dislocation of the Shoulder Complicating Regional Anesthesia | <i>Donald Pagden, Anni S. Halaburt, Romuald Wirpszo, and Andrzej Karyn</i> | 1063 |
| A Serious Complication due to Gastrointestinal Malfunction in a Patient with Myotonic Dystrophy | <i>Yumiko Ishizawa, Hiroshi Yamaguchi, Shuji Dohi, and Kanji Koyama</i> | 1066 |
| Lumbar Epidural Anesthesia for Operative and Postoperative Pain Relief in Infants and Young Children | <i>Bernard Dalens, Alain Tanguy, and Jean-Pierre Haberer</i> | 1069 |
| Cardiovascular Collapse in an Infant after Caudal Anesthesia with a Lidocaine-Epinephrine Solution | <i>Naoki Matsumiya, Shuji Dohi, Hiroshi Takahashi, Yoichi Kondo, and Hiroshi Naito</i> | 1074 |
| Infiltration of a Neuromuscular Relaxant in Diagnosis and Treatment of Torticollis | <i>Eugesse Cremonesi and Kazuko Nakai Murata</i> | 1077 |
| Total Airway Occlusion and Superior Vena Cava Syndrome in a Child with an Anterior Mediastinal Tumor | <i>Dennis R. Northrip, Bradford K. Bohman, and Kentaro Tsueda</i> | 1079 |
| Junctional Rhythm Can Mimic Air Embolism during Precordial Doppler Monitoring | <i>Said S. Azad, David Maguire, and Michael E. Goldberg</i> | 1083 |
| Spontaneous Cardiac Herniation after Pneumonectomy | <i>Chris M. Weinlander, Martin D. Abel, and Jeffrey M. Piehler</i> | 1085 |

LETTERS TO THE EDITOR

- | | | |
|---|---|------|
| A Method for Monitoring Pulse Rate Changes during Test Doses of Epidural Anesthetic Solutions in Obstetrics | <i>Don Daniels and Mark A. Rosen</i> | 1089 |
| Midazolam as an Intravenous Induction Agent in the Elderly | <i>John W. Dandee, N. James Halliday, and Kenneth W. Harper</i> | 1089 |

LETTERS TO THE EDITOR—*continued*

Spinal and Epidural Anesthesia in Patients with the Acquired Immunodeficiency Syndrome	<i>Ernest R. Greene Jr</i>	1090
Safety of Lacri-Lube®	<i>D. Stephen Robins</i>	1091
A Regional Anesthetic Technique Compared to General Anesthesia for Outpatient Knee Arthroscopy	<i>René Martin, Bruno Petit, and Jorge Basora</i>	1091
Transtracheal Jet Ventilation during Fiberoptic Intubation under General Anesthesia	<i>Anis Baraka</i>	1091
Loss of Resistance Technique for Transaortic Celiac Plexus Block	<i>Gary S. Feldstein, Steven D. Waldman, and Mark L. Allen</i>	1092

BOOK REVIEWS

Anesthesia and Sedation in the Dental Office. Raymond A. Dionne and Daniel M. Laskin, eds.	<i>Sanford L. Klein</i>	1094
Cardiac Catheterization and Angiography (3rd ed.). William Grossman, ed.	<i>William J. Greeley</i>	1094
Muscle Relaxants: Basic and Clinical Aspects. Ronald L. Katz, ed.	<i>Martin D. Sokoll</i>	1095
Head Injury and the Anaesthetist. W. Fitch and J. Barker, eds.	<i>Michael M. Todd</i>	1095
Matters of Life and Death: Risks vs Benefits of Medical Care. Eugene D. Robin.	<i>William K. Hamilton</i>	1096
A Guide for Authors		1097

PATIENT	O.R.	SERVICE	TIME
O'Leary	1	CV	7:45
oskowitz	2	CV	7:30
Tennings	3	CV	8:15
Traviotti	4	CV	7:45
Miller	5	GI	8:00
Foley	6	Gen	9:00

SUFENTA®

(sufentanil citrate) Injection 

anesthesia for longer, more stressful procedures



Available in 1 ml, 2 ml, 5 ml ampoules; boxes of ten

Before prescribing, please consult complete prescribing information, of which the following is a brief summary.

CAUTION: Federal Law Prohibits Dispensing Without Prescription.

DESCRIPTION: SUFENTA is a sterile, preservative free, aqueous solution containing sufentanil citrate equivalent to 50 µg per ml of sufentanil base for intravenous injection. The solution has a pH range of 3.5-6.0.

INDICATIONS AND USAGE: SUFENTA (sufentanil citrate) is indicated: As an analgesic adjunct in the maintenance of balanced general anesthesia. As a primary anesthetic agent for the induction and maintenance of anesthesia with 100% oxygen in patients undergoing major surgical procedures, such as cardiovascular surgery or neurosurgical procedures in the sitting position, to provide favorable myocardial and cerebral oxygen balance or when extended postoperative ventilation is anticipated. SEE DOSAGE CHART FOR MORE COMPLETE INFORMATION ON THE USE OF SUFENTA.

CONTRAINDICATIONS: SUFENTA is contraindicated in patients with known hypersensitivity to the drug.

WARNINGS: SUFENTA should be administered only by persons specifically trained in the use of intravenous anesthetics and management of the respiratory effects of potent opioids.

An opioid antagonist, resuscitative and intubation equipment and oxygen should be readily available.

SUFENTA may cause skeletal muscle rigidity, particularly of the truncal muscles. The incidence and severity of muscle rigidity is dose related. Administration of SUFENTA may produce muscular rigidity with a more rapid onset than that seen with fentanyl. SUFENTA may produce muscular rigidity that involves the skeletal muscles of the neck and extremities. The incidence can be reduced by: 1) administration of up to 1/4 of the full paralyzing dose of a non-depolarizing neuromuscular blocking agent just prior to administration of SUFENTA at dosages of up to 8 µg/kg, 2) administration of a full paralyzing dose of a neuromuscular blocking agent following loss of consciousness when SUFENTA is used in anesthetic dosages (above 8 µg/kg) titrated by slow intravenous infusion, or, 3) simultaneous administration of SUFENTA and a full paralyzing dose of a neuromuscular blocking agent when SUFENTA is used in rapidly administered anesthetic dosages (above 8 µg/kg). The neuromuscular blocking agent should be compatible with the patient's cardiovascular status. Adequate facilities should be available for postoperative monitoring and

ventilation of patients administered SUFENTA. It is essential that these facilities be fully equipped to handle all degrees of respiratory depression.

PRECAUTIONS: General: The initial dose of SUFENTA should be appropriately reduced in elderly and debilitated patients. The effect of the initial dose should be considered in determining supplemental doses. Vital signs should be monitored routinely. Nitrous oxide may produce cardiovascular depression when given with high doses of SUFENTA (see CLINICAL PHARMACOLOGY). The hemodynamic effects of a particular muscle relaxant and the degree of skeletal muscle relaxation required should be considered in the selection of a neuromuscular blocking agent. High doses of pancuronium may produce increases in heart rate during SUFENTA-oxygen anesthesia. Bradycardia has been reported infrequently with SUFENTA-oxygen anesthesia and has been responsive to atropine. Respiratory depression caused by opioid analgesics can be reversed by opioid antagonists such as naloxone. Because the duration of respiratory depression produced by SUFENTA may last longer than the duration of the opioid antagonist action, appropriate surveillance should be maintained. As with all potent opioids, profound analgesia is accompanied by respiratory depression and diminished sensitivity to CO₂ stimulation which may persist into or recur in the postoperative period. Appropriate postoperative monitoring should be employed to ensure that adequate spontaneous breathing is established and maintained prior to discharging the patient from the recovery area. Interaction with Other Central Nervous System Depressants: Both the magnitude and duration of central nervous system and cardiovascular effects may be enhanced when SUFENTA is administered to patients receiving barbiturates, tranquilizers, other opioids, general anesthetics or other CNS depressants. In such cases of combined treatment, the dose of one or both agents should be reduced. Head Injuries: SUFENTA may obscure the clinical course of patients with head injuries. Impaired Respiration: SUFENTA should be used with caution in patients with pulmonary disease, decreased respiratory reserve or potentially compromised respiration. In such patients, opioids may additionally decrease respiratory drive and increase airway resistance. During anesthesia, this can be managed by assisted or controlled respiration. Impaired Hepatic or Renal Function: In patients with liver or kidney dysfunction, SUFENTA should be administered with caution due to the importance of these organs in the metabolism and excretion of SUFENTA.

Carcinogenesis, Mutagenesis and Impairment of Fertility: No long-term animal studies of SUFENTA have been performed to evaluate carcinogenic potential. The micronucleus test in female rats revealed that single intravenous

OPERATION	ANESTHESIOLOGIST	SURGEON
Coronary Bypass	Craig/Alvarez	Hodman
Intracranial Aneurysm	Lefcourt/Davies	D'Andrea
Total Hysterectomy	Sanford/Dewey	Higginson
LT. Total Hip Replacement	Connell/Schwartz	Bennett
Anterior Resection of Sigmoid Colon	Cohen/Rothman	Sydney
Thyroidectomy	Jane/Collins	Labadie

doses of SUFENTA as high as 80 µg/kg (approximately 2.5 times the upper human dose) produced no structural chromosome mutations. The Ames *Salmonella typhimurium* metabolic activating test also revealed no mutagenic activity. See ANIMAL TOXICOLOGY for reproduction studies in rats and rabbits.

Pregnancy Category C: SUFENTA has been shown to have an embryocidal effect in rats and rabbits when given in doses 2.5 times the upper human dose for a period of 10 days to over 30 days. These effects were most probably due to maternal toxicity (decreased food consumption with increased mortality) following prolonged administration of the drug. No evidence of teratogenic effects have been observed after administration of SUFENTA in rats or rabbits. There are no adequate and well-controlled studies in pregnant women. SUFENTA should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Labor and Delivery: There are insufficient data to support the use of SUFENTA in labor and delivery. Therefore, such use is not recommended.

Nursing Mothers: It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when SUFENTA is administered to a nursing woman.

Pediatric Use: The safety and efficacy of SUFENTA in children under two years of age undergoing cardiovascular surgery has been documented in a limited number of cases.

Animal Toxicology: The intravenous LD₅₀ of SUFENTA is 16.8 to 18.0 mg/kg in mice, 11.8 to 13.0 mg/kg in guinea pigs and 10.1 to 19.5 mg/kg in dogs. Reproduction studies performed in rats and rabbits given doses of up to 2.5 times the upper human dose for a period of 10 to over 30 days revealed high maternal mortality rates due to decreased food consumption and anoxia, which preclude any meaningful interpretation of the results.

ADVERSE REACTIONS: The most common adverse reactions of opioids are respiratory depression and skeletal muscle rigidity. See CLINICAL PHARMACOLOGY, WARNINGS and PRECAUTIONS on the management of respiratory depression and skeletal muscle rigidity. The most frequent adverse reactions in clinical trials involving 320 patients administered SUFENTA were: hypotension (7%), hypertension (3%), chest wall rigidity (3%) and bradycardia (3%). Other adverse reactions with a reported incidence of less than 1% were: **Cardiovascular:** tachycardia, arrhythmia; **Gastrointestinal:** nausea, vomiting; **Respiratory:** apnea, postoperative respiratory depression, bronchospasm; **Dermatological:** itching, erythema; **Central Nervous System:** chills; **Miscellaneous:** intraoperative muscle movement.

DRUG ABUSE AND DEPENDENCE: SUFENTA (sufentanil citrate) is a Schedule II controlled drug substance that can produce drug dependence of the morphine type and therefore has the potential for being abused.

OVERDOSAGE: Overdosage would be manifested by an extension of the pharmacological actions of SUFENTA (see CLINICAL PHARMACOLOGY) as with other potent opioid analgesics. However, no experiences of overdosage with SUFENTA have been established during clinical trials. The intravenous LD₅₀ of SUFENTA in male rats is 9.34 to 12.5 mg/kg (see ANIMAL TOXICOLOGY for LD₅₀s in other species). Intravenous administration of an opioid antagonist such as naloxone should be employed as a specific antidote to manage respiratory depression. The duration of respiratory depression following overdosage with SUFENTA may be longer than the duration of action of the opioid antagonist. Administration of an opioid antagonist should not preclude more immediate countermeasures. In the event of overdosage, oxygen should be administered and ventilation assisted or controlled as indicated for hypoventilation or apnea. A patent airway must be maintained, and a nasopharyngeal airway or endotracheal tube may be indicated. If depressed respiration is associated with muscular rigidity, a neuromuscular blocking agent may be required to facilitate assisted or controlled respiration. Intravenous fluids and vasopressors for the treatment of hypotension and other supportive measures may be employed.

DOSAGE AND ADMINISTRATION: The dosage of SUFENTA should be individualized in each case according to body weight, physical status, underlying pathological condition, use of other drugs, and type of surgical procedure and anesthesia. In obese patients (more than 20% above ideal total body weight), the dosage of SUFENTA should be determined on the basis of lean body weight. Dosage should be reduced in elderly and debilitated patients (see PRECAUTIONS).

world leader in anesthesia research



**JANSSEN
PHARMACEUTICA**

Janssen Pharmaceutica Inc.
Piscataway, NJ 08854
© Janssen Pharmaceutica Inc. 1986

U.S. Patent No. 3,998,834
761,604-M
January 1986, March 1986

JPI-698

**Albumin & PPF
are no safer
or more
effective than
Hespan[®]**

(hetastarch)

...they're simply

As safe as albumin or PPF

In comparative clinical studies, platelet counts, hematocrits, serum fibrinogen levels, prothrombin times (PT), and partial thromboplastin times (PTT) seen with Hespan were comparable to those seen with albumin or plasma protein fraction (PPF).^{1,2}

Other studies demonstrate that when any reduction in platelet count or prolongation of PT or PTT does occur with Hespan, no increased bleeding results, even in patients with multiple trauma.³⁻⁵ As with any volume expander, patients should be monitored for excessive hemodilution of coagulant factors or circulatory overload when large volumes are administered.

When Hespan-treated patients were monitored to detect localized or

systemic sepsis, there was no evidence of a decrease in their ability to ward off infection or combat an established infection.⁵

Hespan is nonantigenic and, as with blood-derived colloids, any risk of allergic reaction is minimal. Hespan also has a negligible effect on subsequent blood typing or cross-matching.⁶

As effective as albumin or PPF

Comparative clinical studies have repeatedly demonstrated that Hespan is as effective as albumin or PPF in postoperative myocardial revascularization,¹⁻³ and hemorrhagic, traumatic, or septic shock.^{4,5,7}

No significant differences between Hespan and albumin or PPF were noted in any efficacy parameter.^{1-5,7} Hespan effectively maintained colloid osmotic pressure, restored plasma volume, and improved cardiac output and renal function in hypovolemic patients.^{1-5,7} And, the volume-expanding effect of a single infusion of Hespan can persist for 24 hours or longer.

Half the price of albumin or PPF

Hespan offers a potential savings to your hospital of tens of thousands of dollars a year.

double the price.



For additional information, contact the Medical Services Department, American Critical Care, 1600 Waukegan Road, McGaw Park, IL 60085. Phone 1-800-323-4980.

**Lifesaving,
moneysaving**



HESPAN[®]
(hetastarch)

American Critical Care

American Hospital Supply Corporation

Please see references and brief summary of prescribing information on following page.

References: 1. Diehl JT, Lester JL, Cosgrove DM: Clinical comparison of hetastarch and albumin in postoperative cardiac patients. *Ann Thorac Surg* 34 (6):674-679, 1982. 2. Moggio RA, Rha CC, Somberg ED, et al: Hemodynamic comparison of albumin and hydroxyethyl starch in postoperative cardiac surgery patients. *Crit Care Med* 11 (12):943-945, 1983. 3. Kirklén JK, Lell WA, Kouchoukos NT: Hydroxyethyl starch versus albumin for colloid infusion following cardiopulmonary bypass in patients undergoing myocardial revascularization. *Ann Thorac Surg* 37 (1):40-46, 1984. 4. Puri VK, Paidipaty B, White L: Hydroxyethyl starch for resuscitation of patients with hypovolemia and shock. *Crit Care Med* 9 (12):833-837, 1981. 5. Shatney CH, Deepika K, Miliello PR, et al: Efficacy of hetastarch in the resuscitation of patients with multisystem trauma and shock. *Arch Surg* 118:804-809, 1983. 6. Daniels MJ, Strauss RG, Smith-Floss AM: Effects of hydroxyethyl starch on erythrocyte typing and blood crossmatching. *Transfusion* 22 (3):226-228, 1982. 7. Rackow EC, Falk JL, Fein IA, et al: Fluid resuscitation in circulatory shock: A comparison of the cardiorespiratory effects of albumin, hetastarch, and saline solutions in patients with hypovolemic and septic shock. *Crit Care Med* 11(11):839-850, 1983.

HESPAN® (hetastarch)

6% Hetastarch in 0.9% Sodium Chloride Injection

CONTRAINDICATIONS

Hetastarch is contraindicated in patients with severe bleeding disorders or with severe congestive cardiac and renal failure with oliguria or anuria.

WARNINGS

Large volumes may alter the coagulation mechanism. Thus, administration of hetastarch may result in transient prolongation of prothrombin, partial thromboplastin and clotting times. With administration of large doses, the physician should also be alert to the possibility of transient prolongation of bleeding time.

Hematocrit may be decreased and plasma proteins diluted excessively by administration of large volumes of hetastarch.

Usage in Leukapheresis: Significant declines in platelet counts and hemoglobin levels have been observed in donors undergoing repeated leukapheresis procedures due to the volume expanding effects of hetastarch. Hemoglobin levels usually return to normal within 24 hours. Hemodilution by hetastarch and saline may also result in 24 hour declines of total protein, albumin, calcium and fibrinogen values.

Usage in Pregnancy: Reproduction studies have been done in mice with no evidence of fetal damage. Relevance to humans is not known since hetastarch has not been given to pregnant women. Therefore, it should not be used in pregnant women, particularly during early pregnancy, unless in the judgment of the physician the potential benefits outweigh the potential hazards.

Usage in Children: No data available pertaining to use in children.

The safety and compatibility of additives have not been established.

PRECAUTIONS

The possibility of circulatory overload should be kept in mind. Special care should be exercised in patients who have impaired renal clearance since this is the principal way in which hetastarch is eliminated. Caution should be used when the risk of pulmonary edema and/or congestive heart failure is increased. Indirect bilirubin levels of 0.83 mg% (normal 0.0-0.7 mg%) have been reported in 2 out of 20 normal subjects who received multiple hetastarch infusions. Total bilirubin was within normal limits at all times; indirect bilirubin returned to normal by 96 hours following the final infusion. The significance, if any, of these elevations is not known; however, caution should be observed before administering hetastarch to patients with a history of liver disease.

Regular and frequent clinical evaluation and laboratory determinations are necessary for proper monitoring of hetastarch use during leukapheresis. Studies should include CBC, total leukocyte and platelet counts, leukocyte differential count, hemoglobin, hematocrit, prothrombin time (PT), and partial thromboplastin time (PTT).

Hetastarch is nonantigenic. However, allergic or sensitivity reactions have been reported (see ADVERSE REACTIONS). If such reactions occur, they are readily controlled by discontinuation of the drug and, if necessary, administration of an antihistaminic agent.

ADVERSE REACTIONS

The following have been reported: vomiting, mild temperature elevation, chills, itching, submaxillary and parotid glandular enlargement, mild influenza-like symptoms, headaches, muscle pains, peripheral edema of the lower extremities, and anaphylactoid reactions consisting of periorbital edema, urticaria, and wheezing.

HOW SUPPLIED

NDC 0094-0037-05-Hespan® (6% Hetastarch in 0.9% Sodium Chloride Injection) is supplied sterile and nonpyrogenic in 500 ml intravenous infusion bottles.

CAUTION

Federal (U.S.A.) law prohibits dispensing without prescription.

Rev. Feb., 1982

Distributed by

American Critical Care

American Hospital Supply Corporation
McGaw Park, IL USA 60085



The Latest News on Drug Disposition

Perspectives in Clinical Pharmacology

Editor: **Milo Gibaldi, Ph.D.**

School of Pharmacy
University of Washington
Seattle, Washington

Perspectives in Clinical Pharmacology reports the most recent advances in drug research and clinical practice, offering a broad perspective that stresses basic underlying pharmacokinetic principles. Each issue presents one main article and one or two short regular features. Articles discuss the principles of pharmacokinetics, drug disposition, and therapeutics of individual drugs, drug classes, and disease entities.

Perspectives in Clinical Pharmacology is a vital new source of information for:

- clinical pharmacologists
- clinical and hospital pharmacists
- drug development scientists
- academic pharmaceutical scientists
- biochemists who use pharmacokinetic principles in their work

A Sample of Recent Topics:

- β -Blockers vs. Weight Reduction in Hypertension
- Serum Level and Cardiac Monitoring after an Acute Overdose
- Combining Oral Antiarrhythmics
- Dietary Proteins and Allopurinol Elimination

Perspectives in Clinical Pharmacology

Volume 4 (12 issues), 1986 0737-2914 \$60.00

Subscription price includes postage and handling in the U.S., and Canada. Add \$21.00 for airmail delivery to Europe; add \$24.00 for airmail delivery to the rest of the world.

Sample copies are available.

For sample copies, send to
in North and South America:
Elsevier Science Publishing Co., Inc.
P.O. Box 1663
Grand Central Station
New York, NY 10163-1663

in the rest of the world:
Elsevier Science Publishers
Direct Mail Department
P.O. Box 211
1000 AE Amsterdam
The Netherlands

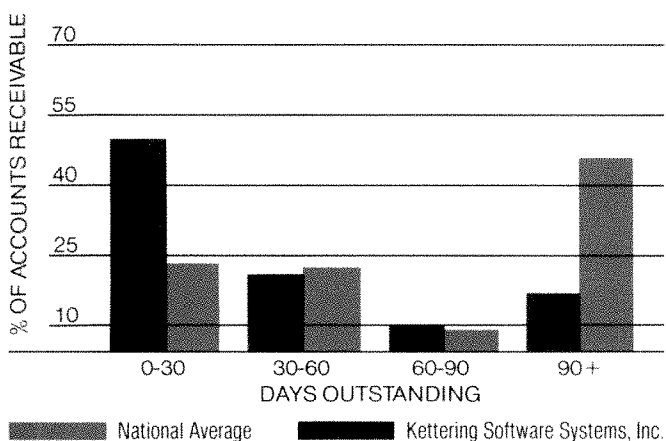
Note: Send subscription orders to either your usual supplier or the New York address. Subscriptions entered upon receipt of payment. Subscription rates valid through Dec. 31, 1986.

Before you buy any Anesthesia Software Package read this:

The Kettering Anesthesia Software Package (ASP) will put you in control of your accounts...and control of your accounts is the most effective way to maintain close to 100% collection percentage. The Kettering Software ASP System is a billing system designed specifically for the anesthesiologist by a team of anesthesiologists and computer programmers.

Ask yourself if your practice is collection healthy...with a 93% collection rate or better...Kettering Software installations are helping group practices around the country manage their practice better and improve their collection efforts up to better than 93% of billings.

Account control is the key to the Kettering System.



The Kettering System gives control over an individual account from its entry into the system through claims processing and patient inquiry, right down to the pre-collection notification. The system automatically calculates the anesthesia charge based on time, modifiers, and the basic unit value of the procedure. This information is combined with the patient demographics to generate either a standard AMA claim form or to initiate an electronic transmittal to selected insurance carriers. After initial payment has been received, ASP will

automatically balance bill the secondary insurance if applicable. The quality that sets this system apart from the rest is account control and the guarantee that you can maximize your cash flow.

Kettering Systems Software people are ASA key contacts, always working to keep the ASP system ahead of the industry and its needs, and talking with legislators regularly about government actions to further the causes of the professional anesthesiologist. Want more information? Use the coupon for descriptive literature or write or call us today. We promise fast action.

Name _____

Address _____

City _____ State _____ Zip _____

Phone _____ Best Time? _____

SEE US AT ASA BOOTH # 656 IN LAS VEGAS



KETTERING SOFTWARE SYSTEMS, INC.

2773 Orchard Run Road
Dayton, Ohio 45449
(513) 435-6135 1-800-221-5584

Specializing in Anesthesia Practice Management

IARS MEMBERSHIP

FOR YOUR IN-TRAINING AND CONTINUING MEDICAL EDUCATION

The International Anesthesia Research Society is a non-profit, scientific and educational corporation of the State of Ohio, founded in 1922 "to foster progress and research in anesthesia." To this end the Society

Publishes the oldest journal in the specialty, *Anesthesia and Analgesia*

Sponsors an annual scientific meeting (Congress) which is held in March each year

Funds anesthesia-related research through the IARS B.B. Sankey Anesthesia Advancement Award

Membership in the IARS is voluntary; it is also separate and distinct from membership in any other local, state, regional or national anesthesia organization or association. Membership is open to individuals who qualify in the various categories shown below; who complete the appropriate application and submit it to the IARS Cleveland office with the applicable dues. All memberships include a subscription to *Anesthesia and Analgesia*. Members and Associate Members are entitled to a reduced registration fee at the IARS annual meeting; Educational Members pay no registration fee.

. . . . MEMBERSHIP CATEGORIES

MEMBERSHIP: Open to individuals with doctorate degrees, who are licensed to practice in the medical, osteopathic, dental or veterinary medicine fields (i.e., MD, MB, DO, DDS, DMD, DVM); and to individuals with doctorate degrees in any scientific discipline (PhD), who are engaged in academic, private or commercial research.

ASSOCIATE MEMBERSHIP: Open to individuals in the allied health professions, duly certified by their professional accrediting organization as nurse anesthetists (CRNA); respiratory therapists or technicians (RRT or CRTT); physician/anesthesia assistants (PA/MMS); and other allied health professionals in anesthesia-related practice.

Annual Dues for Members and Associate Members: \$50.00 U.S.; \$61.00 foreign.

These memberships are entered on a calendar year basis only.

EDUCATIONAL MEMBERSHIP: Open (with certification by program director) to doctors (interns/residents) enrolled in anesthesiology training programs; nurses enrolled in nurse anesthesia schools; students enrolled in programs leading to certification as physician assistants, respiratory therapists or technicians

Annual Dues for Educational Members: One-half of member rate. These memberships are entered in January or July for 2, 3, or 4 year periods. Applications, certified by program directors, must accompany check to cover full membership period.

International Anesthesia Research Society
3645 Warrensville Center Road, Cleveland, Ohio 44122, USA

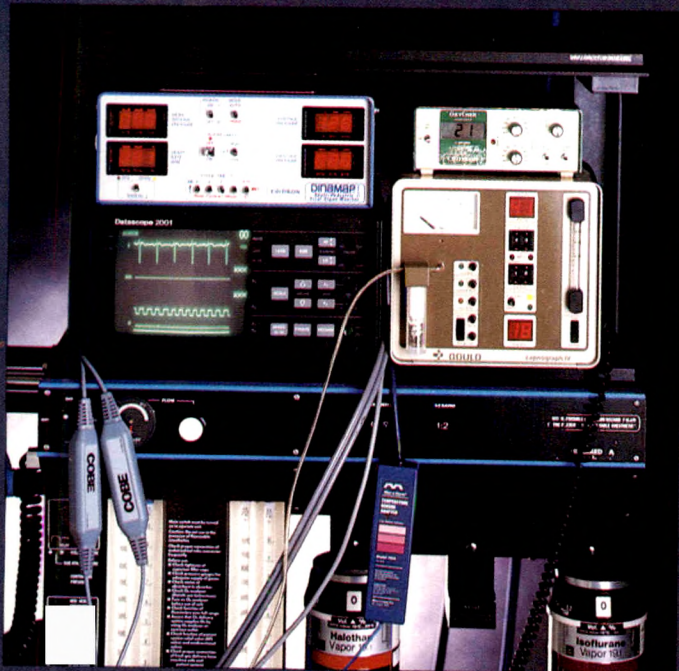
Please send me _____ application(s) for: Membership (_____)
Associate Membership (_____)
Educational Membership (_____)

Please print clearly: _____
Name and Degree (MD, DO, CRNA, RN, RRT, etc.)

Street Address

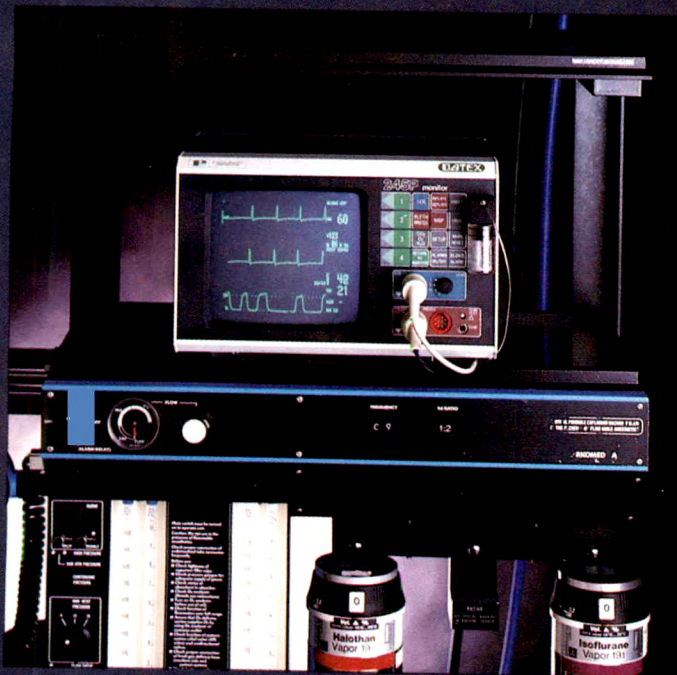
City, State, Zip Code (country)

No Matter How You Stack It, The Others Just Don't Measure Up



One of the most pressing problems facing the anesthesiologist today is space. As more and more instruments are brought into the O.R. providing new and important parameters, it is clear that there just isn't enough room. The complexity of the problem is heightened by the need to learn and operate individually dedicated stand alone monitors, each designed by different manufacturers.

Introducing The PB245 Cardiac/Airway Gas Monitor



The PB245 Cardiac/Airway Gas Monitor represents a major breakthrough by integrating, into a single compact monitor, the essential parameters for patient monitoring. It combines basic cardiac measurements of ECG, temperature and blood pressure, both invasive and non-invasive, with important analysis of the airway gases of CO₂, O₂ and N₂O. Simple to operate, the PB245 can display numerical data as well as real time waveforms and trends. It also has the flexibility to be a totally non-invasive monitor, yet has the ability to measure invasive pressure as well.

Today, Puritan-Bennett Corporation offers you a better way to monitor in the O.R. — the PB245 Cardiac/Airway Gas Monitor.

For more information or to arrange for a demonstration, contact your nearest sales representative or call 1-800-255-6773.

HELPING YOU MANAGE RISK IN THE O.R.

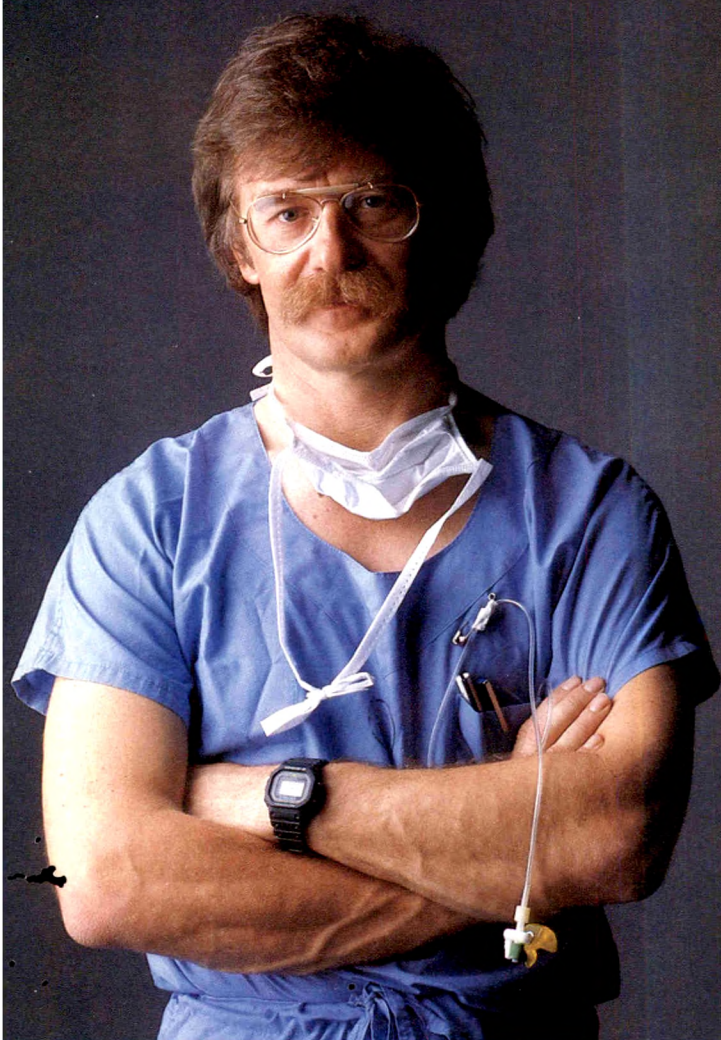
Distributor in western hemisphere



PURITAN-BENNETT
CORPORATION

Boston Division
265 Ballardvale Street
Wilmington, MA 01887
(617) 657-8655

Sophisticated Knowledge



Anesthesiology is the point at which medicine and technology must precisely converge. And as medicine and technology move forward, the task of maintaining the focus becomes ever more challenging.

At Physio-Control, we believe that our responsibility is to design instruments that meet the demands of both the physical and technical environment. We must communicate as well as measure.

Physio-Control Corporation
Redmond, WA 98073-9706 USA
Toll Free: Outside Washington, 800/426-8047
Inside Washington, 800/562-8071

©1986 Physio-Control Corporation.

**PHYSIO
CONTROL**

For the management
of a growing
patient population

ANAESTHESIA IN THE ELDERLY

Harold T. Davenport, M.B., Ch.B.

Consultant Anaesthetist
Park Hospital and Clinical Research Centre
Harrow, England

More and more geriatric patients are coming into the operating room. **Anaesthesia in the Elderly** addresses the many problems that an anesthesiologist needs to understand for the safe and practical management of these patients.

This book focuses on the medical and surgical problems associated with the elderly, and discusses management from a variety of viewpoints, including assessment, anesthetic administration, and post-operative care.

Additional topics include: common operation anesthesia, apparatus, monitoring and drugs, diagnostic and therapeutic procedures, and resuscitation.

To receive a copy of this vital guide to geriatric patient management, contact your local bookseller or order directly from Elsevier at the address below.

1986 195 pages 0-444-01047-5 paper \$19.50

(Available outside North America from
William Heinemann Medical Books, U.K.)

Note: Price subject to change without notice.

Please allow 6-8 weeks for delivery.

Send to your usual supplier or:

in North America:

Elsevier Science Publishing Company, Inc.
P.O. Box 1663, Grand Central Station
New York, New York 10163-1663

Elsevier

3 86

EB367



Now Published by Elsevier:

Journal of the American Geriatrics Society

GENE H. STOLLERMAN, MD
Editor
Boston University Hospitals
Boston, MA

JOHN P. BLASS, MD, PhD
Associate Editor
White Plains, NY

Journal of the American Geriatrics Society has been providing the medical community with outstanding original coverage of all aspects of geriatrics for over 30 years. Emphasizing original research, *Journal of the American Geriatrics Society* publishes both clinical and basic science studies on a broad range of topics. A distinguished editorial board, drawn from a wide variety of medical specialties, ensures the accuracy, high quality, and noteworthiness of every contribution selected for publication.

Regular features of *Journal of the American Geriatrics Society* include:

- **Medical Ethics and Humanities**
thought-provoking viewpoints on the difficult ethical questions facing all physicians who treat the elderly
- **Law and Public Policy**
clear, concise reports on the latest legislative and judicial developments that affect patient management
- **Clinical Experience**
practical solutions to common problems in geriatric health care

Geriatricians, internists, cardiologists, rheumatologists, psychiatrists, endocrinologists, family practitioners, and others who treat aging patients rely on *Journal of the American Geriatrics Society* for up-to-date information on all aspects of geriatric health care.

Journal of the American Geriatrics Society is abstracted/indexed in *Index Medicus*, *Current Contents*, *Science Citation Index*, *Automatic Subject Citation Alert*, *Social Sciences Citation Index*, and *ISI/Biomed*.

1986 Subscription Information:

Journal of the American Geriatrics Society

Volume 34, 12 issues, 1986

Institutional Rate: \$75.00

Personal Rate: \$65.00

For air delivery in the U.S., Canada, and Mexico, add \$28.00. Subscribers outside the U.S. should add \$13.00 for surface delivery (not available to Europe); \$17.00 for surface air lift delivery to Europe; \$55.00 for air delivery to the rest of the world; \$29.00 for surface air-lift delivery to Japan.

Sample copies are available.
ISSN 0002-8614

For sample copies, send to

in North and South America:
Elsevier Science Publishing Co., Inc.
P.O. Box 1663
Grand Central Station
New York, NY 10163-1663

in the rest of the world:
Elsevier Science Publishers
Direct Mail Department
P.O. Box 211
1000 AE Amsterdam
The Netherlands

Note: Send subscription orders to either your usual supplier or the New York address. All subscriptions begin with the first issue of the calendar year. Subscription rates valid through Dec. 31, 1986.

1 86

EB361

Sophisticated Oximetry



The new Physio-Control LIFESTAT® 1600 Pulse Oximeter. Much easier to read and interpret. Temperature compensated sensor. Electrosurgical filtration so that it can maintain accuracy without interference. Portable and battery or line operated so that it can follow the patient to the recovery room.

The Physio-Control LIFESTAT 1600 Pulse Oximeter. A new generation in accuracy, reliability and function. Carefully designed to help you do an even better job.

Physio-Control Corporation
Redmond, WA 98073-9706 USA
Toll Free: Outside Washington, 800/426-8047
Inside Washington, 800/562-8071

©1986 Physio-Control Corporation.

**PHYSIO
CONTROL**

INTERNATIONAL ANESTHESIA RESEARCH SOCIETY

THE B.B. SANKEY ANESTHESIA ADVANCEMENT AWARD

1986 Awards

The Board of Trustees of the IARS is pleased to advise that four Awards were granted and announced at the March 1986 meeting in Las Vegas, as follows:

Zeljko J. Bosnjak, PhD, Medical College of Wisconsin, Milwaukee, WI:

"Effects of Chronic Administration of Calcium Antagonists"

John F. Butterworth IV, MD, Bowman Gray School of Medicine, Winston-Salem, NC:

"Brain Cellular Mechanisms of Increased Anesthetic Susceptibility with Aging"

Philippe R. Housmans, MD, PhD, Mayo Foundation, Rochester, MN:

"Influence of Halothane on Intracellular Calcium Handling in Mammalian Cardiac Muscle"

Vladimir Nigrovic, MD, Medical College of Ohio, Toledo, OH:

"Adverse Reactions and Metabolism of Atracurium"

1987 B.B. SANKEY ANESTHESIA ADVANCEMENT AWARD

Applications for up to \$25,000 are invited for the 1987 Award, subject to the following basic conditions:

- The proposal must be within the general field of anesthesiology and may be for research, clinical care, education, or administration.
- The applicant must be a member of the International Anesthesia Research Society.
- Applications must be received in the IARS Cleveland office no later than December 15, 1986.
- The official application for the Award must be used. This form, as well as the guidelines for applicants, is available on request to:

International Anesthesia Research Society
3645 Warrensville Center Rd.
Cleveland, OH 44122
Telephone: (216) 295-1124

The 1987 Award(s) will be announced at the Annual Scientific Meeting (61st Congress) of the International Anesthesia Research Society to be held at the Buena Vista Palace, Lake Buena Vista (Orlando), Florida, March 14-18, 1987.

Introducing the only fiberscope
designed for the anesthesiologist.

Olympus LF-1



OLYMPUS
SUPERIORITY YOU CAN SEE.

The Olympus LF-1 Intubation Scope designed specifically for:

- problem intubations
- double lumen tube placement
- endotracheal tube changes
- preoperative airway assessment
- evaluation of upper airway damage

The LF-1
incorporates
features most
requested by
anesthesiologists*

60cm working length (longer than a bronchoscope) accommodates all oral and nasal intubation techniques used in your hospital, making the LF-1 truly versatile.

Thin 4mm insertion tube allows you to pass the LF-1 through all double lumen endobronchial tubes and endotracheal tubes even as small as 5mm. But the LF-1 is firm enough to prevent buckling should you choose a larger ET tube.

Superior optics. You'll appreciate how the increased image size, high resolution and 75° field of view simplify identification of anatomic structures and orientation within the pharynx.

1.2mm channel gives you additional versatility for instilling anesthetics and removing secretions.

Balanced tip deflection lets you choose the intubating position that's most comfortable for you.

Lightweight control section allows convenient thumb-operated tip deflection with either hand.

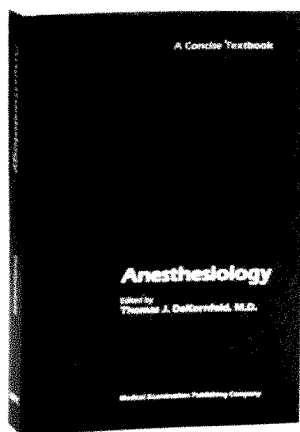
Full immersibility assures you of 100% cleaning and disinfecting. If you choose, the LF-1 can also be safely gas sterilized.

Affordable. With all its advantages, the LF-1 is priced substantially below a bronchoscope.



OLYMPUS
SUPERIORITY YOU CAN SEE.

Olympus Corporation
Medical Instrument Division
4 Nevada Drive
Lake Success, New York 11042
800-342-1673



ANESTHESIOLOGY: A CONCISE TEXTBOOK

Edited by **Thomas J. DeKornfeld, M.D.**

Professor of Anesthesiology
Professor of Postgraduate Medicine
and Health Professions Education
Department of Anesthesiology
University of Michigan, Ann Arbor

Here in one volume, twenty-five experts in anesthesiology combine their knowledge in one readable authoritative source. Clinicians will find, in an easily accessible format, a complete and current overview of the clinical applications of anesthesiology as well as the underlying theory. Five major sections detail the practice of anesthesiology; anesthesia and the surgical specialties; anesthesia and systemic problems; anesthesiology as a specialty; and tables and formulas. Discussing areas not usually covered in standard texts, such as legal considerations, ethical questions, and economic aspects of anesthesiology, this book makes an excellent quick reference for the practicing anesthesiologist.

1986

576 pages

0-444-01010-6

paper

\$33.95

CONTENTS

PART I THE SPECIALTY OF ANESTHESIOLOGY

History of Anesthesiology
Education in Anesthesiology
Ethical Questions in the Clinical Practice of Anesthesiology
Legal Considerations in Anesthesiology
Economic Aspects of Anesthesiology
Practice Patterns in Anesthesiology
Nurse Anesthesia and the Anesthesia Care Team

PART II THE PRACTICE OF ANESTHESIOLOGY

Theories of Narcosis
Patient Assessment — Preoperative Visit
Anesthetic Techniques
The Pharmacology of Drugs Used in Anesthesiology

Monitoring Under Anesthesia
Computers and Anesthesia
Respiratory Care
The Recovery Room

PART III ANESTHESIA FOR THE SURGICAL SPECIALTIES

Anesthesia for General Surgery
Anesthesia for Thoracic Surgery
One-Lung Anesthesia
Anesthesia for Cardiac Surgery
Anesthesia for Vascular Surgery
Anesthesia for Orthopedic Surgery
Anesthesia for Urologic Surgery
Anesthesia for Head and Neck Surgery
Anesthesia for Ophthalmic Surgery
Anesthesia for Neurosurgery
Anesthesia for Gynecologic Surgery
Anesthesia for Obstetrics
Anesthesia for Pediatric Surgery

PART IV ANESTHESIA ON THE BASIS OF PATIENT PROBLEMS

The Patient with a Difficult Airway
The Patient with Ischemic Heart Disease Undergoing Noncardiac Surgery
The Patient with Pulmonary Disease
The Patient with Kidney Disease
The Patient with Gastrointestinal and Liver Disease
The Patient with Metabolic Disease
The Patient with Trauma
The Patient with Fluid Imbalance
The Patient with Chronic Pain

PART V MISCELLANEOUS

Reading the Scientific Literature
Equations, Formulas, and Physical Characteristics
Normal Laboratory Values

INDEX

Order from your usual supplier or:

MEPC/A division of Elsevier • P.O. Box 1663, Grand Central Station • New York, New York 10163-1663

Note: Price subject to change without notice.

Medical Examination Publishing Company* is a division of Elsevier Science Publishing Company, Inc., New York, NY.

Take an esophageal stethoscope, incorporate a Doppler ultrasound probe that monitors aortic blood flow, and you have continuous cardiac output monitoring from Lawrence.

The Lawrence 3000® Continuous Cardiac Output Monitor is your best defense, your greatest patient safeguard,

in surgery. It gives you continuous hemodynamic information, allowing faster reaction times and earlier warnings of hemorrhage, myocardial depression or adverse drug reaction.

The Lawrence 3000 continuously monitors cardiac output, cardiac index and systemic vascular resistance. It sets up in min-

utes. And gives you trouble-free monitoring throughout surgery.

Systemic vascular resistance is based on operator input of BP, or an automatic line transfer from an independent BP monitor.

After setup a periodic adjustment may be needed — usually less than once an hour.

Every Lawrence 3000 moni-

Think of it as a continuously moni

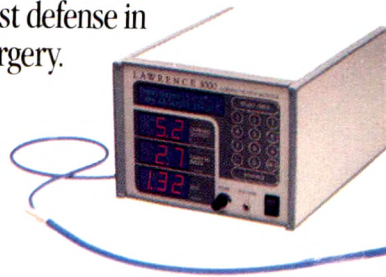


tor comes with in-service training by an experienced professional. Plus instructional videos, clinical studies and operational manuals to help educate your OR staff.

Call Lawrence Medical, Customer Service Department, at 1-800-247-4499 or 1-206-881-1300 (collect in Washington), for a free demonstration, video

tape or information package.

Discover how the Lawrence 3000 can be your best defense in surgery.

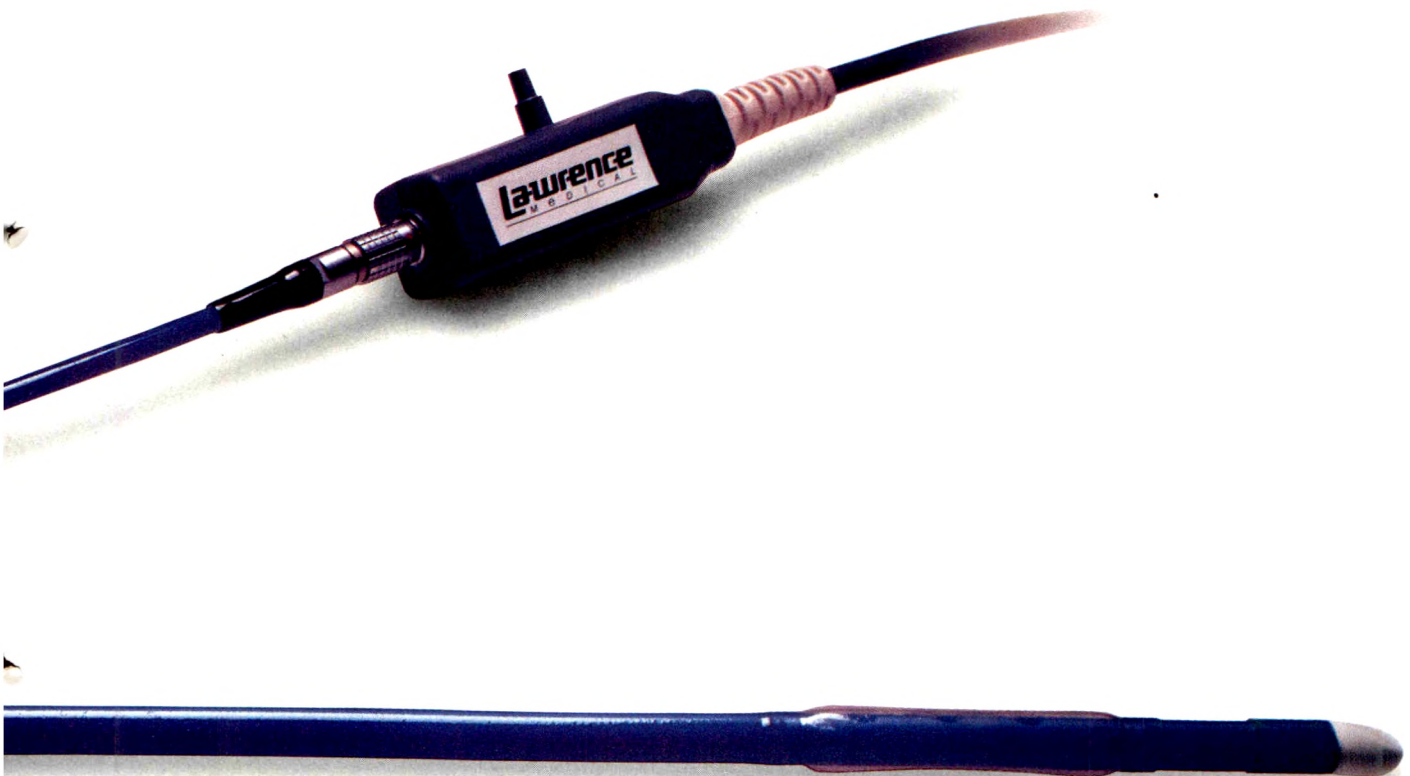


Continuous cardiac output monitoring from the company who invented it.

Lawrence
M E D I C A L

14910 N.E. 31st Circle
Redmond, Washington 98052
1-800-247-4499
In Washington, call collect:
(206) 881-1300

stethoscope that tors cardiac output.



Anaquest

Enlon[®]

(edrophonium chloride
injection, USP)

**A rapid-acting
neuromuscular reversal agent**

From the developers of
Ethrane[®] (enflurane) **and Forane[®]** (isoflurane)

Anaquest
2005 West Beltline Highway
Madison WI 53713 2318
608 273 0019 800 ANA DRUG
A Division of BOC Inc



P24586

60-second reversal of neuromuscular blockade

- **Onset of reversal significantly faster than with neostigmine or pyridostigmine**—60 seconds versus 7 minutes for neostigmine, 12 minutes for pyridostigmine.^{1,2}
- **Duration of reversal comparable to that of neostigmine**—66 minutes versus 76 minutes for neostigmine.^{1,2}
- **Significantly fewer muscarinic side effects and lower atropine requirement than with neostigmine**—edrophonium, 0.5 mg/kg, with only 7 μ g/kg atropine, produced minimal change in heart rate or mean arterial pressure compared to noticeable changes in both indexes following neostigmine, 0.04 mg/kg, using twice the atropine dose (15 μ g/kg).^{1,2}
- **May be the preferred reversal agent for atracurium and vecuronium**
“...compared with neostigmine, edrophonium has a more complete spectrum of atracurium reversal characteristics, and...antagonizes more rapidly residual atracurium-induced neuromuscular blockade.”³
“Edrophonium may in fact be the preferred reversal agent for routine use with [vecuronium], having the advantages that restoration of voluntary muscle function is very rapid, and that the relatively small dose of atropine required minimizes the unwanted side-effects of this drug.”⁴

***Note:** When duration of action is adjusted for differences in onset of action, the relative durations are 65 minutes for edrophonium, and 69 minutes for neostigmine.

1. Cronnelly R, Morris RB, Miller RD: Edrophonium: duration of action and atropine requirement in humans during halothane anesthesia. *Anesthesiology* 57:261-266, 1982. 2. Miller RD, et al: Comparative times to peak effect and duration of action of neostigmine and pyridostigmine. *Anesthesiology* 41:27-33, 1974. 3. Jones RM, Pearce AC, Williams JP: Recovery characteristics following antagonism of atracurium with neostigmine or edrophonium. *Br J Anaesth* 56:453-457, 1984. 4. Baird WLM, Bowman WC, Kerr WJ: Some actions of ORG NC45 and of edrophonium in the anaesthetized cat and in man. *Br J Anaesth* 54:375-385, 1982.

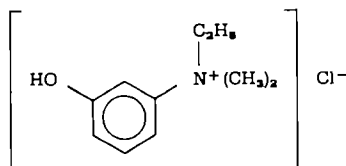
Please see use information on next page.

Anaquest

Enlon[®] (edrophonium chloride injection, USP)

DESCRIPTION

ENLON (edrophonium chloride injection, USP) is a rapid acting cholinergic (cholinesterase inhibitor). Chemically edrophonium chloride is ethyl (m-hydroxyphenyl) dimethylammonium chloride and its structural formula is:



ENLON contains in each mL of sterile solution:

10 mg edrophonium chloride compounded with 0.46% phenol and 0.2% sodium sulfite as preservative, buffered with sodium citrate and citric acid. Its pH is adjusted to approximately 5.4.

CLINICAL PHARMACOLOGY

ENLON (edrophonium chloride injection, USP) activates neuromuscular transmission primarily by inhibiting or inactivating acetylcholinesterase. By inactivating the acetylcholinesterase enzyme, acetylcholine is not hydrolyzed by acetylcholinesterase and is thereby allowed to accumulate. The accumulation of acetylcholine at the sites of cholinergic transmission facilitates transmission of impulses across the myoneural junction.

INDICATIONS AND USAGE

ENLON (edrophonium chloride injection, USP) is recommended as a reversal agent or antagonist of nondepolarizing muscle relaxants such as tubocurarine, metocurine, atracurium, vecuronium, or pancuronium. It is not effective against depolarizing relaxants such as succinylcholine and decamethonium. It is also useful if used adjunctively in the treatment of respiratory depression caused by curare overdose. ENLON is recommended for use in the differential diagnosis of myasthenia gravis. It may also be used as an adjunct to evaluate treatment requirements of the disease, and for evaluating emergency treatment in myasthenic crisis. It is not recommended for maintenance therapy in myasthenia gravis.

CONTRAINDICATIONS

ENLON (edrophonium chloride injection, USP) is not to be used in patients with known hypersensitivity to anticholinesterase agents, or in patients having urinary obstructions of mechanical type.

WARNINGS

It is recommended that 1 mg atropine sulfate should be made available for immediate use, to counteract any severe cholinergic reaction. ENLON (edrophonium chloride injection, USP) should be used with caution in patients with bronchial asthma or cardiac dysrhythmias. Transient bradycardia may occur and be relieved by atropine sulfate. Isolated instances of cardiac and respiratory arrest following administration of edrophonium chloride have been reported. It is postulated that these are vagotonic effects.

PRECAUTIONS

General: As with any antagonist of nondepolarizing muscle relaxants, adequate recovery of voluntary respiration and neuromuscular transmission must be obtained prior to discontinuation of respiratory assistance. Should a patient develop "anticholinesterase insensitivity" for brief or prolonged periods, the patient should be carefully monitored and the dosage of anticholinesterase drugs reduced or withheld until the patient again becomes sensitive to them.

Drug Interactions: The drug should not be administered prior to the administration of any nondepolarizing muscle relaxants. The drug should be administered with caution to patients with symptoms of myasthenic weakness who are also on anticholinesterase drugs. Anticholinesterase overdose (cholinergic crisis) symptoms may mimic underdose (myasthenic weakness) so the use of this drug may worsen the condition of these patients (see OVERDOSAGE section for treatment).

Pregnancy Category C: It is not known whether ENLON (edrophonium chloride injection, USP) can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity, since there have been no adequate and well controlled studies in humans.

Labor and Delivery: The effect of ENLON on the mother and fetus, on the duration of labor or delivery, on the possibility that forceps delivery or other intervention or resuscitation of the newborn will be necessary is not known. The effect of the drug on the later growth, development and functional maturation of the child is also unknown.

Nursing Mothers: The safety of ENLON during lactation in humans has not been established.

ADVERSE REACTIONS

A patient in myasthenic crisis, being treated with ENLON (edrophonium chloride injection, USP) should be observed for bradycardia or cardiac standstill and cholinergic reactions if an overdose is given. Reactions common to anticholinesterase agents such as edrophonium chloride are:

Cardiovascular: arrhythmias (especially bradycardia), fall in output leading to hypotension;

Respiratory: increased tracheobronchial secretions, laryngospasm, bronchiolar constriction and respiratory muscle paralysis;

Neurologic: convulsions, dysarthria, dysphonia, and dysphagia;

Gastrointestinal: nausea, vomiting, increased peristalsis, increased gastric and intestinal secretions, diarrhea, abdominal cramps;

Musculoskeletal: weakness and fasciculations;

Miscellaneous: increased urinary frequency, diaphoresis, increased lacrimation, pupillary constriction, diplopia, and conjunctival hyperemia.

OVERDOSAGE

Muscarinic-like symptoms (nausea, vomiting, diarrhea, sweating, increased bronchial and salivary secretions and bradycardia) may appear with overdose (cholinergic crisis) of ENLON (edrophonium chloride injection, USP) but may be managed by the use of atropine. Obstruction of the airway by bronchial secretions can arise and may be managed with suction (especially if tracheostomy has been performed) and by the use of atropine. Signs of atropine overdose such as dry mouth, flush and tachycardia should be avoided as tenacious secretions and bronchial plugs may form. Should edrophonium chloride overdose occur:

1. Maintain respiratory exchange.
2. Monitor cardiac function.

Appropriate measures should be taken if convulsions or shock are present.

DOSEAGE AND ADMINISTRATION

The recommended adult intravenous injection for antagonism of neuromuscular blocks:

Administer 1 mL (10 mg) slowly within a period of 30 to 45 seconds, the dosage may be repeated to a maximum total dose of 4 mL (40 mg). Its onset of action is manifest within 30 to 60 seconds after injection. Response should be monitored carefully and assisted ventilation should always be employed. When given to counteract muscle relaxant overdose, the dose effect on respiration should be observed prior to repeat dosages and assisted ventilation should be employed.

ENLON (edrophonium chloride injection, USP) Test in Differential Diagnosis of Myasthenia Gravis:

Adults:

Intravenous Dose: Prepare a tuberculin syringe with 1 mL (10 mg) of ENLON and an intravenous needle; intravenously inject 0.2 mL (2 mg) within 15 to 30 seconds. The needle should be left in situ. If a cholinergic reaction (muscarinic side effects, skeletal muscle fasciculations and increased muscle weakness) occurs, discontinue test and intravenously administer 0.4 mg to 0.5 mg atropine sulfate. Inject the remaining 0.8 mL (8 mg) only if no reaction occurs after 45 seconds. The test may be repeated after one-half hour.

Intramuscular Dose: Intramuscularly inject 1 mL (10 mg) of ENLON. If hyperreactivity (cholinergic reaction) is demonstrated, repeat the patient after one-half hour with another intramuscular injection of 0.2 mL (2 mg) ENLON. This will eliminate the possibility of false-negative reactions.

Children:

Intravenous dose in children weighing up to 75 pounds:

Intravenously inject 0.1 mL (1 mg) ENLON. If there is no response within 45 seconds, incremental doses of 0.1 mL (1 mg) given every 30 to 45 seconds may be administered to a maximum total dose of 0.5 mL (5 mg). The recommended dose in infants is 0.05 mL (0.5 mg).

Intravenous dose in children weighing above 75 pounds:

Intravenously inject 0.2 mL (2 mg) ENLON. If there is no response within 45 seconds, incremental doses of 0.1 mL (1 mg) given every 30 to 45 seconds may be administered to a maximum total dose of 1 mL (10 mg).

Intramuscular Dose: Intramuscularly inject 0.2 mL (2 mg) ENLON in children weighing up to 75 pounds; above this weight, the dose is 0.5 mL (5 mg). All signs of hyperreactivity (cholinergic reaction) noted in the intravenous test will be demonstrated in the intramuscular test; however, there is a two to ten minute delay before reaction.

ENLON (edrophonium chloride injection, USP) Test to Evaluate Treatment Requirements in Myasthenia Gravis:

The test dose of ENLON should follow one hour after oral intake of the drug being used to treat the disease. The recommended dose is 0.1 mL to 0.2 mL (1 mg to 2 mg) administered intravenously. Response to ENLON test dose in treated myasthenic patients is summarized as follows:

Undertreated patient: Myasthenic response; characterized by increased muscle strength (ptosis, diplopia, dysphonia, dysphagia, dysarthria, respiration, limb strength). This indicates inadequate treatment of the myasthenic condition.

Controlled patient: Adequate response; characterized by no change in muscle strength with minimal side reactions (lacrimation, diaphoresis, salivation, abdominal cramps, nausea, vomiting, diarrhea). Fasciculations (orbicularis oculi, facial muscles, limb muscles) may or may not occur. The response indicates that therapy is stabilized.

Over-treated patient: Cholinergic response; characterized by decreased muscle strength and severe side reactions. Fasciculations may be observed. This response occurs in myasthenics who have been over-treated with anticholinesterase drugs.

ENLON (edrophonium chloride injection, USP) Test in Crisis:

Crisis in the myasthenic patient is characterized as a state of severe respiratory distress with inadequate ventilatory exchange, and unpredictable response to medication. If the patient is apneic, achieve ventilatory exchange immediately to avoid cardiac arrest and irreversible central nervous system damage.

The ENLON Test should not be conducted until respiratory exchange is maintained. The cholinergic patient will exhibit further weakness in the muscles of respiration and will have increased oropharyngeal secretions if ENLON is administered. Whereas, upon administration of ENLON the myasthenic patient will demonstrate improved respiration and can be given additional medication. To perform the test prepare a syringe with 0.2 mL (2 mg) ENLON and intravenously inject 0.1 mL (1 mg). The patient's cardiac and respiratory actions should be observed for change. The remaining 0.1 mL (1 mg) may be injected after one minute if no response is noted. If, after the entire 0.2 mL (2 mg) dose has been injected, no improvement in respiration occurs, discontinue all anticholinesterase drugs. Controlled ventilation can be achieved by tracheostomy with assisted respiration.

HOW SUPPLIED

ENLON (edrophonium chloride injection, USP):

NDC 10019-873-15 15 mL multidose vials.

in the SHERIDAN™ a full range of choice.

A Leading Family of Tracheal Tube Products.

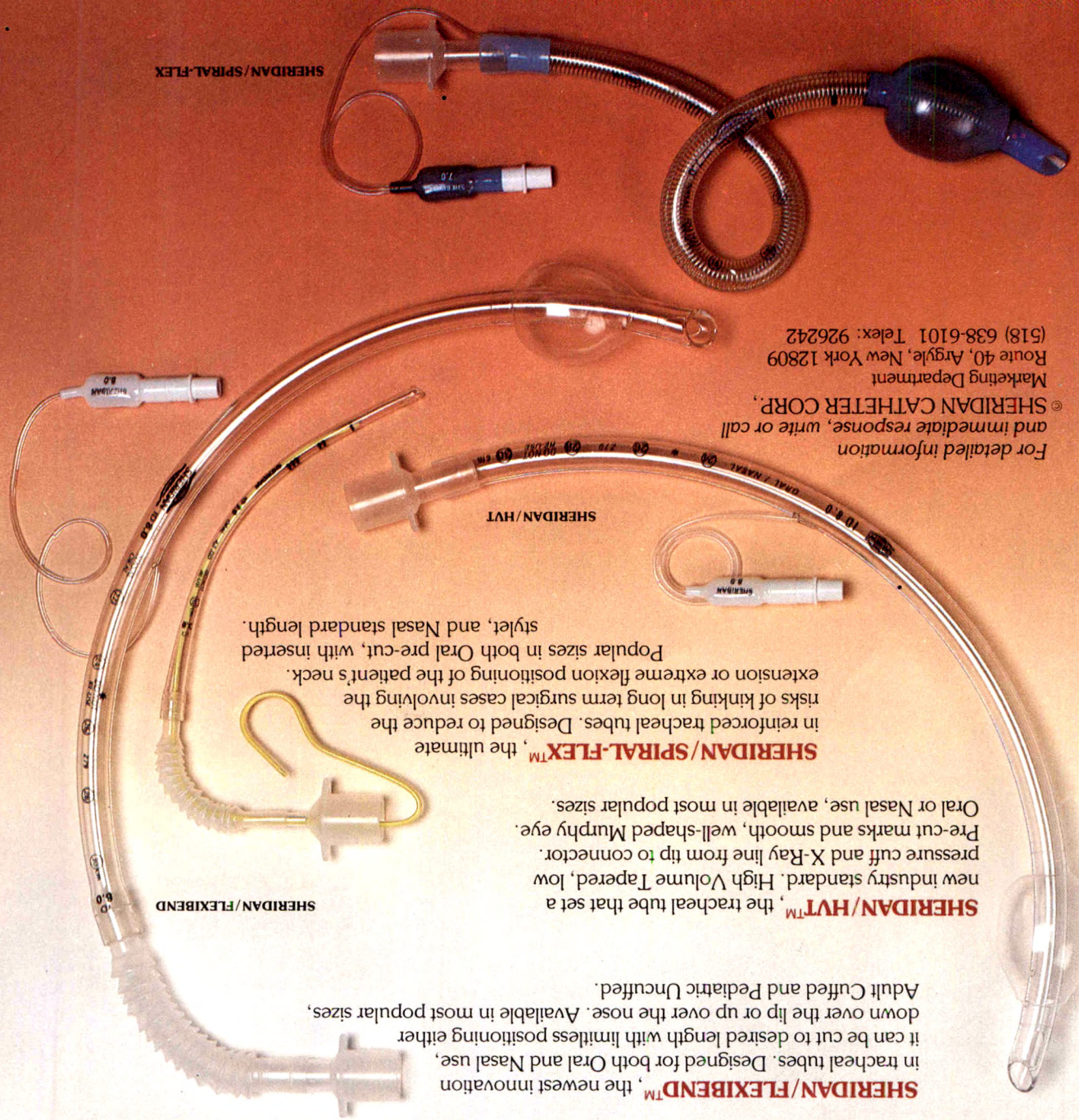
From the established innovator in design and manufacturing, Sheridan Catheter Corp. offers the widest selection with uncompromising quality and unique features for patient and user convenience. From Pediatric to Adult needs, with specialty kits and accessories, Sheridan has tracheal tubes to meet almost any medical application.

SHERIDAN/FLEXIBEND™, the newest innovation in tracheal tubes. Designed for both Oral and Nasal use, it can be cut to desired length with limitless positioning either down over the lip or up over the nose. Available in most popular sizes, Adult Cuffed and Pediatric Uncuffed.

SHERIDAN/HVT™, the tracheal tube that set a new industry standard. High Volume Tapered, low pressure cuff and X-Ray line from tip to connector. Pre-cut marks and smooth, well-shaped Murphy eye. Oral or Nasal use, available in most popular sizes.

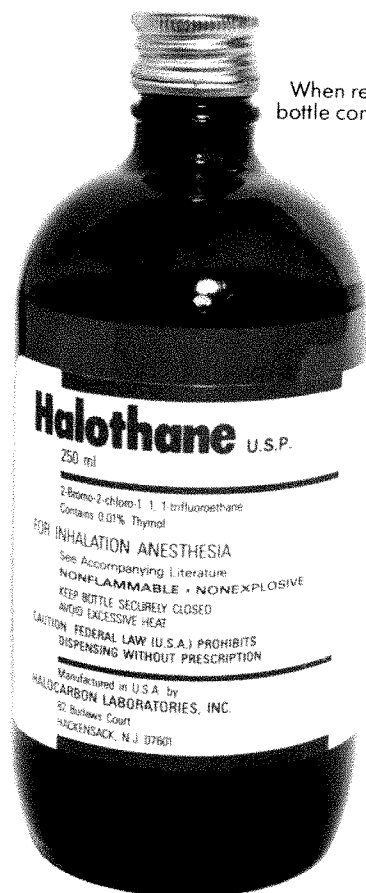
SHERIDAN/SPIRAL-FLEX™, the ultimate in reinforced tracheal tubes. Designed to reduce the risks of kinking in long term surgical cases involving the extension or extreme flexion positioning of the patient's neck. Popular sizes in both Oral pre-cut, with inserted stylet, and Nasal standard length.

For detailed information
and immediate response, write or call
© SHERIDAN CATHETER CORP.,
Marketing Department
Route 40, Argyle, New York 12809
(518) 638-6101 Telex: 926242



HALOTHANE U.S.P.

Produced by
Halocarbon Laboratories, Inc.



When requested
bottle comes with collar.

- First Maker of Fluorinated Anesthetics in the U.S.A.
- Pioneer in Anesthetic Purity
- Lowest Price of Any Potent Anesthetic

HALOCARBON
LABORATORIES, INC.

P.O. Box 833
Hackensack, NJ 07602
(201) 343-8703

IARS REVIEW COURSE LECTURES AVAILABLE

— 1986, 60th Congress—26 Review
Course Lectures—\$6.00

— 1985, 59th Congress—26 Review
Course Lectures—\$6.00

— 1984, 58th Congress—24 Review
Course Lectures—\$6.00

— 1983, 57th Congress—16 Review
Course Lectures—\$5.00

— 1982, 56th Congress—14 Review
Course Lectures—\$5.00

To:
International Anesthesia Research Society
3645 Warrensville Center Road
Cleveland, Ohio 44122

Please send Lecture Booklets checked above.

My check, payable to IARS in the amount of
\$_____ is enclosed.

(Name)

(Mail Address)

(City, State, Zip)

The Influence of Hepatic Plasma Flow on Alfentanil Plasma Concentration Plateaus Achieved with an Infusion Model in Humans:

Measurement of Alfentanil Hepatic Extraction Coefficient

M. Chauvin, MD, F. Bonnet, MD, C. Montembault, MD, J. C. Levron, PhD, and P. Viars, MD

CHAUVIN M, BONNET F, MONTEBAULT C, LEVRON JC, VIARS P. The influence of hepatic plasma flow on alfentanil plasma concentration plateaus achieved with an infusion model in humans: measurement of alfentanil extraction coefficient. *Anesth Analg* 1986;65:999-1003.

In a group of seven patients undergoing intracranial surgery under neurolept anesthesia, an alfentanil infusion was initiated with a loading dose of 235 $\mu\text{g/kg}$ over 5 min, followed by a maintenance infusion rate of 1.8 $\mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$ in order to obtain a steady state plasma concentration (C_{ss}) of 400 ng/ml according to an infusion model. The mean values of C_{ss} ($446 \pm 209 \text{ ng/ml}$) were close to the predicted ones. Nevertheless, an important intersubject variability in C_{ss} values was observed. A positive linear correlation existed

between alfentanil steady state clearance and indocyanine green clearance ($r = 0.88$) and between alfentanil steady state clearance and cardiac index ($r = 0.93$). In three patients, a catheter was inserted into an hepatic vein to determine the alfentanil hepatic extraction coefficient. Alfentanil plasma clearance did not differ from alfentanil hepatic clearance and alfentanil hepatic extraction coefficient values ranged from 0.32-0.53. We conclude that alfentanil is a drug with an intermediate hepatic extraction coefficient and that alfentanil plasma clearance depends on hepatic plasma flow, which is thus one of the factors accounting for individual variability in plasma concentration plateaus achieved with an infusion model.

Key Words: ANALGESICS—alfentanil. ANESTHETICS, INTRAVENOUS—alfentanil. PHARMACOKINETICS—alfentanil.

The pharmacokinetic properties of alfentanil suggest that the drug may be administered by continuous infusion (1,2). To calculate infusion regimens and predicted plasma concentration, the distribution and elimination of the drug must be estimated (3,4). Compared with other opiates, alfentanil has a small distribution volume and a short elimination half-life (1,5,6) despite a plasma clearance one-half that of fentanyl (2). Alfentanil is almost completely eliminated by hepatic metabolism (2); however, the hepatic extraction coefficient of alfentanil has never been measured. When estimated from plasma clearance (2), the hepatic extraction coefficient of alfentanil has an intermediate value of between 0.3 and 0.5, suggesting that both changes in hepatic blood flow and in metabolic activ-

ity could alter alfentanil clearance (7,8). During anesthesia, hepatic plasma flow (HPF) is diminished (9), possibly reducing plasma clearance of alfentanil and thus modifying the steady state plasma concentration (C_{ss}) achieved with an infusion regimen.

For these reasons, we aimed to examine the influence of HPF on alfentanil clearance under neurolept anesthesia. Hepatic plasma flow was estimated by measuring the indocyanine green (ICG) clearance in a group of patients and was directly measured in three additional patients after hepatic vein catheterization. In this second group, the alfentanil hepatic extraction coefficient was also measured directly and compared with the indirect method of measurement.

Methods

Seven patients, two women and five men, aged 20-58 years, (37 ± 15 , mean \pm SD) underwent anesthesia for cerebral surgery. None of the patients had renal, hepatic, or cardiovascular disease. Informed consent

Received from the Department of Anesthesiology, Hôpital de la Pitié, Paris, France.

Address correspondence to Dr. Chauvin, Département d'Anesthésie, Hôpital Ambroise Paré, 9 Avenue Charles de Gaulle, 92100 Boulogne sur Seine, France. Accepted for publication May 9, 1986.

was obtained from each patient at the preoperative visit, and the protocol was approved by the ethical committee of the University of Paris VI. All patients were given oral diazepam, 10 mg, 2 hr before induction. Anesthesia was induced with thiopental 7 mg/kg intravenously; succinylcholine, 1 mg/kg, was given to facilitate tracheal intubation. Anesthesia was maintained with droperidol (0.3 ± 0.1 mg/kg) and 60% N₂O in oxygen delivered by mechanical ventilation. Arterial blood gas tensions were measured at the beginning of anesthesia and during the operation; minute ventilation was adjusted as necessary to maintain the arterial CO₂ tension between 35 and 40 mm Hg. Alfentanil was given intravenously 5–10 min after thiopental administration. The opiate injection was preceded by 80 μ g/kg of pancuronium to prevent chest wall rigidity, and full muscle paralysis was further assured with additional pancuronium, up to a total dose of 0.12 ± 0.03 mg/kg. Alfentanil was administered as a loading dose followed by a continuous infusion, via a syringe pump (Vial®). The loading dose and the maintenance infusion rate (MIR) of alfentanil were determined according to the method of Wagner (4) in order to obtain a C_{ss} of 400 ng/ml, as follows:

$$\begin{aligned} \text{MIR} &= C_{ss} \times \text{plasma clearance} \\ \frac{\text{loading dose}}{\text{MIR}} &= \frac{t_{1/2}\beta}{T} \times 1.443 \end{aligned}$$

where $t_{1/2}\beta$ is the half-life elimination and T is the duration of the initial infusion.

The mean values of $t_{1/2}\beta$ given in previous kinetic studies (1,5,6,10–13), being 90 min, and the mean values of plasma clearance being 4.5 ml·min⁻¹·kg⁻¹, the loading dose of alfentanil was calculated as 235 μ g/kg for 5 min and the MIR as 1.8 μ g·kg⁻¹·min⁻¹. The maintenance infusion rate was continued until the end of surgery. In all patients, a thermistor tipped Swan–Ganz catheter and a radial artery catheter were inserted before the induction of anesthesia, to monitor the hemodynamic parameters. Cardiac output was determined by the thermodilution method and cardiac index was calculated. Central temperature was monitored with the Swan–Ganz catheter thermistor and maintained between 36.0°C and 37.0°C by a warming blanket.

Serial blood samples were obtained from the radial artery catheter during the opioid infusion for measurement of alfentanil concentrations. Sampling times were before the loading dose, then at 5, 15, 30, and every 30 min after the start of the infusion in order to measure C_{ss}; C_{ss} values were determined as the average of three samples withdrawn at 30-min inter-

vals; the steady state plasma level was attained when the three plasma concentrations were within a 10% range. Alfentanil steady state clearance was calculated by dividing the MIR by the C_{ss} (4). Alfentanil concentrations were determined by radioimmunoassay, with a sensitivity of 100 pg/ml (14). The free fraction (unbound fraction) of alfentanil was measured by equilibrium dialysis at a concentration of 50 and 500 ng/ml using purified tritium labeled alfentanil, as previously described (11).

The estimated HPF was determined using indocyanine green (ICG) as an indicator. In this study, two methods were used for the measurement of ICG clearance. The single intravenous bolus method was used in four patients (group A) with a dose of 0.5 mg/kg administered over 10 sec in all patients. Arterial blood samples were withdrawn before and 2, 4, 6, and 8 min after the ICG bolus injection, to determine the plasma concentration of ICG using a spectrometric method (15). Optical density units were converted to plasma concentrations by reference to standard curves of dye in plasma constructed with each dye lot and found to be linear in the concentration range used in the present study. The coefficient of variation of aliquots of normal plasma was 1.5%. In all patients, plasma ICG concentration declined monoexponentially ($r > 0.98$, $P < 0.01$). The log-concentration vs time curve was computed in order to obtain a straight line. The concentration at time zero (C₀) was extrapolated. The ICG volume of distribution (Vd) was calculated as Vd = (injected dose)/C₀. Indocyanine green clearance was computed as the product of the Vd multiplied by the elimination rate constant (K) of the curve according to the following equation: CL = VdK. The constant intravenous infusion method was used in three other patients (group B) for the measurement of ICG clearance. A loading dose of 20 mg of ICG was followed by a constant infusion of 30 mg/hr. Indocyanine green clearance was calculated as the infusion rate per min divided by the ICG C_{ss}, where the ICG C_{ss} was the mean value of six arterial samples, collected every 2 min at steady state. This steady state was assumed to be 20 min after starting the ICG infusion (16). In these three patients, a catheter (Cordis 7 F) was inserted before anesthesia into an hepatic vein, under fluoroscopic control, in order to determine ICG and alfentanil hepatic extraction coefficients, which are the fractions of ICG and alfentanil extracted by the liver. Hepatic venous samples of ICG and alfentanil were collected simultaneously with arterial samples. The hepatic extraction coefficients of the substances were calculated from the value of the plasma concentrations in arterial (C_a) and in hepatic venous blood (C_{hv}) as follows: (C_a - C_{hv})/C_a. HPF

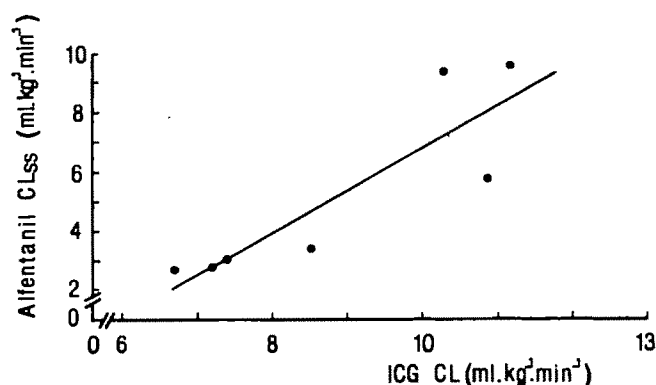


Figure 1. Plot of indocyanine green clearance (ICG CL) and alfentanil steady state plasma clearance (alfentanil CLss) measured simultaneously ($r = 0.88$, $P < 0.01$).

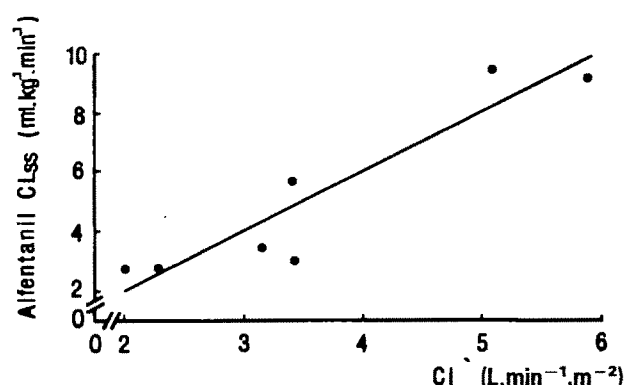


Figure 2. Plot of cardiac index (CI) and alfentanil steady state plasma clearance (alfentanil CLss) measured simultaneously ($r = 0.93$, $P < 0.01$).

was calculated as infusion rate per min divided by $(C_a - C_{iv})$ and alfentanil hepatic clearance as $HPF \times$ alfentanil hepatic extraction coefficient.

Cardiac index was calculated as the mean of five measurements in group A and seven measurements in group B. Measurements were taken every 2 min and only values within a 10% range were used. Cardiac index and ICG clearance determinations were performed simultaneously at 30 min intervals during alfentanil infusion, and blood samples were collected for alfentanil C_{ss} measurements.

Data are expressed as mean \pm SD. Linear regression analysis was performed.

Results

The C_{ss} of alfentanil was obtained at 30 min after the start of the MIR in four patients and at 60 min after the start of the MIR in three patients. In each patient, C_{ss} variability did not exceed 5%. The difference between the three ICG clearances and the three cardiac index measurements, taken when the alfentanil C_{ss} was achieved, was less than 10% for all patients. Alfentanil C_{ss} averaged 446 ± 209 ng/ml; an important intersubject variability was observed in the values of C_{ss} . A significant positive correlation was observed between alfentanil steady state clearance and ICG clearance (alfentanil steady state clearance = 1.41 ICG clearance - 7.33 ; $r = 0.88$, $P < 0.01$) (Fig. 1). The slope of the linear relationship between ICG clearance and alfentanil steady state clearance was situated between 0.58 and 2.24, with a confidence limit of 95%. A significant positive correlation also was observed between alfentanil steady state clearance and cardiac index (alfentanil steady state clearance = 2.04 cardiac index - 2.09 ; $r = 0.93$, $P < 0.01$) (Fig. 2).

The results of three patients undergoing hepatic

catheterization are summarized in Table 1. The three ICG hepatic extraction coefficient measurements performed during the study in each patient were within a 5% range. Alfentanil hepatic extraction coefficients were, respectively, 0.32, 0.50, and 0.53. In these three patients, alfentanil steady state clearances were similar to alfentanil hepatic clearances.

The alfentanil free fraction averaged $16 \pm 1\%$. Individual alfentanil steady state clearances were unrelated to individual free fractions ($r = 0.19$, $n = 7$) of the drug.

Discussion

The method used in the present study to rapidly obtain a constant plasma level was a simple well-known scheme of administration, described by Wagner (4). It consisted of two consecutive infusions; ideally, the first, or rapid infusion, loads the central compartment whereas the second, or slow infusion, maintains the drug concentration at a desired level. This method of approximating constant plasma concentration has been previously used for fentanyl administration during abdominal (17) and cardiac surgery (18). In the present study, a plateau of alfentanil plasma concentration was obtained in all patients. The mean C_{ss} was close to the predicted level. In accordance with Wagner's method (4), a loading dose of alfentanil $235 \mu\text{g/kg}$ administered over 5 min was required to saturate the distribution volume. The loading dose of alfentanil is greater than that determined by Fragen et al. (19) using Mitenko and Ogilvie's method (3). The calculated dose in the present study eliminated the initial decrease in plasma concentration reported by Fragen et al. (19). However, despite the fact that values obtained were close to the predicted mean concentration, great variability existed between patients, as pre-

Table 1. Plasma and Hepatic Clearances of Alfentanil and Indocyanine Green in Patients Undergoing Hepatic Vein Catheterization

Patient	CI (ml·min ⁻¹ ·kg ⁻¹)	ICG HE (%)	HPF (ml·min ⁻¹ ·kg ⁻¹)	ALF CL _{ss} (ml·min ⁻¹ ·kg ⁻¹)	ALF HE (%)	ALF Hepatic CL (ml·min ⁻¹ ·kg ⁻¹)
1	71	55	20.4	9.5	50	10.2
2	77	57	18.1	9.4	53	9.6
3	75	63	11.8	3.0	32	3.8

Abbreviations: CI, individual mean cardiac index; ICG HE, indocyanine green hepatic extraction coefficient; HPF, hepatic plasma flow; ALF CL_{ss}, alfentanil steady state clearance; ALF HE, alfentanil hepatic extraction; ALF Hepatic CL, alfentanil hepatic clearance.

viously observed (19,20). Thus, prediction of C_{ss} for a given patient proves difficult. The wide range of C_{ss} values observed in patients could be explained by the individual pharmacokinetic variability existing within any patient population, including clearance and distribution volumes (1). Indeed, with only the loading dose and the brief MIR used in this study, factors maintaining plasma concentrations constant were clearance and the drug transfer to tissues, because alfentanil was not infused to 3–4 $t_{1/2\beta}$ in any patient, i.e., blood and tissues were never in complete equilibrium (21).

In the present study, alfentanil clearance was determined in steady state conditions. The lack of variation in the three ICG clearance measurements performed in each patient confirmed steady state conditions during this period. The mean steady state clearance of alfentanil in our study agrees with mean values previously reported after a single bolus injection (11–13). In a previous study, which used alfentanil MIR to determine the clearance of the drug, steady state clearance was comparable with an identical range in individual values (20). During the period studied, intersubject variability in steady state clearance values may be related to the same factors affecting C_{ss} , i.e., individual variability in distribution volume and elimination, since steady state clearance is inversely related to C_{ss} . Alfentanil is almost exclusively eliminated by the liver, renal elimination of this drug being very low (2). In our study, the hepatic elimination of alfentanil was confirmed by the similarity between alfentanil steady state clearance and alfentanil hepatic clearance. In previous alfentanil kinetic studies, the alfentanil hepatic extraction coefficient was estimated by dividing the plasma clearance by the HPF, because alfentanil is mainly present in plasma and is weakly transported by red blood cells (2). A value of 0.3 was obtained by Bower and Hull (5) and by Ferrier et al. (11), whereas a higher value of 0.6 was reported in other studies (1,6). However, the alfentanil hepatic extraction coefficient was never measured directly. In our study, using hepatic vein blood samples, we confirmed that alfentanil has an intermediate hepatic ex-

traction coefficient. This intermediate value plays a role in the elimination of the drug; alfentanil elimination is independent of its protein binding because the hepatic extraction coefficient of alfentanil largely exceeds the unbound plasma fraction of the drug (8), but clearance of drugs with an intermediate hepatic extraction coefficient, such as alfentanil, could be dependent on HPF (7,8). For this reason, we investigated the relationship between alfentanil steady state clearance and ICG clearance.

Indocyanine green clearance is often chosen to estimate HPF because of its high hepatic extraction coefficient and absence of biotransformation before excretion in bile. In patients with normal liver function, HPF estimation by measurement of ICG kinetics with single dose or through steady state infusion has showed results identical to those obtained by hepatic vein catheterization (16). Under the conditions of the present study, ICG clearance could also be used as an estimate of HPF since neurolept anesthesia did not appear to compromise hepatic function (22). Furthermore, the ICG hepatic extraction coefficient values were in the same range as those reported in awake patients with normal liver function (16) and ICG hepatic extraction determinations remained constant throughout our study in each of the three patients. Thus the linear significant relationship existing between ICG clearance and alfentanil steady state clearance means that HPF was an important factor in the disposition of alfentanil, despite the short infusion time studied. Hudson and Stanski (23) have shown that metabolic elimination is important in determining the effect of alfentanil, more so than in the case of fentanyl. The greater importance of elimination over redistribution in the duration of action may be explained by the smaller total apparent volume of alfentanil distribution, compared with other opiates. It has been reported to be seven times smaller than that of fentanyl (2). This large difference in the volume of distribution is attributed to the fact that the lipid solubility of alfentanil is 6.6 times less than that of fentanyl (1,2), and to the higher degree of alfentanil protein binding (2), these two factors limiting alfentanil

diffusion into tissues and thus its volume of distribution. A small volume of distribution results in higher plasma concentrations so that more of the drug present in the body is available to the liver for elimination. Thus, for a drug like alfentanil, with such a small volume of distribution, plasma concentration is particularly susceptible to changes in HPF, even when distribution phase is not achieved. Furthermore, HPF has been demonstrated to be cardiac index dependent under neurolept anesthesia (22), which explains the linear relationship between the alfentanil steady state clearance and the cardiac index observed in our experiments. Consequently, in patients monitored with a thermistor tipped Swan-Ganz catheter, it is suggested that simple rearrangement of the regression line equation in Figure 2 enables the use of the cardiac index to estimate the correct alfentanil infusion rate for any desired alfentanil plasma levels, as follows: alfentanil rate = desired alfentanil level (2.04 cardiac index - 2.09). However, it must be emphasized that HPF is only one of the factors affecting the disposition of alfentanil, and that other variables such as hepatic extraction coefficient, volume of distribution, and plasma protein binding have to be considered.

In conclusion, pharmacokinetic models enable the prediction of C_{ss} values in patients but only with a wide individual range. This can be explained by the intersubject variations in pharmacokinetic parameters. Alfentanil can be classified as a drug with an intermediate hepatic extraction coefficient and its elimination is dependent on HPF, and this factor contributes to individual variability in alfentanil pharmacokinetics, especially when plasma concentration plateaus are achieved with an infusion model.

References

1. Bovill JG, Sebel PS, Blackburn CL, Heykants J. The pharmacokinetics of alfentanil (R 39209): a new opioid analgesic. *Anesthesiology* 1982;57:439-43.
2. Stanski DR, Hug CC Jr. Alfentanil—a kinetically predictable narcotic analgesic. *Anesthesiology* 1982;57:435-8.
3. Mitenko PA, Ogilvie RI. Rapidly achieved plasma concentration plateaus, with observation on theophylline kinetics. *Clin Pharmacol Ther* 1972;13:329-35.
4. Wagner JG. A safe method for rapidly achieving plasma concentration plateaus. *Clin Pharmacol Ther* 1974;16:691-700.
5. Bower S, Hull CJ. Comparative pharmacokinetics of fentanyl and alfentanil. *Br J Anaesth* 1982;54:871-901.
6. Camu F, Gepts E, Rucquoi M, Heykants J. Pharmacokinetics of alfentanil in man. *Anesth Analg* 1982;61:657-61.
7. George CF. Drug kinetics and hepatic blood flow. *Clin Pharmacokinet* 1979;4:443-8.
8. Wilkinson GR, Shand DG. A physiological approach to hepatic drug clearance. *Clin Pharmacol Ther* 1975;18:377-90.
9. Gelman SI. Disturbances in hepatic blood flow during anesthesia and surgery. *Arch Surg* 1976;111:881-3.
10. Bentley JB, Borel JD, Nenad RE, Gillespie TJ. Age and fentanyl pharmacokinetics. *Anesth Analg* 1982;61:968-71.
11. Ferrier C, Marty J, Bouffard Y, Haberer JP, Levron JC, Duvaldestin P. Alfentanil pharmacokinetics in patients with cirrhosis. *Anesthesiology* 1985;62:480-4.
12. Haberer JP, Schoeffler P, Couderc E, Duvaldestin P. Fentanyl pharmacokinetics in anesthetized patients with cirrhosis. *Br J Anaesth* 1982;54:1256-70.
13. Helters H, Van Peer A, Woestenborghs R, Noordvin H, Heykants J. Alfentanil kinetics in the elderly. *Clin Pharmacol Ther* 1984;36:239-43.
14. Michiels M, Hendriks R, Heykants J. Radioimmunoassay of the new opiate analgesics alfentanil and sufentanil. Preliminary pharmacokinetic profile in man. *J Pharm Pharmacol* 1983;35:86-93.
15. Wiegand BD, Ketterer SG, Rappaport E. The use of indocyanine green for the evaluation of hepatic function and blood flow in man. *Am J Digestive Dis* 1960;5:427-36.
16. Caesar J, Shaldon S, Chiandussi L, Guevara L, Sherlock S. The use of indocyanine green in the measurement of hepatic blood flow and as a test of hepatic function. *Clin Sci* 1961;21:43-57.
17. Hengstmann JH, Stoeckel H, Schüttler J. Infusion model for fentanyl based on pharmacokinetic analysis. *Br J Anaesth* 1980;52:1021-5.
18. Moldenhauer CC, Hug CC Jr. Continuous infusion of fentanyl for cardiac surgery (abstract). *Anesth Analg* 1982;61:206.
19. Fragen RJ, Booij LHDJ, Braak GJJ, Vree TB, Heykants J, Crul JF. Pharmacokinetics of the infusion of alfentanil in man. *Br J Anaesth* 1983;55:1077-81.
20. Shafer A, White PF, Coe V, Stanski DR. Use of pharmacokinetic variables to determine alfentanil maintenance infusion regimens. *Anesthesiology* 1983;59:A244.
21. Rowland M, Tozer TN. Constant rate intravenous infusion. In: Rowland M, Tozer TN, eds. *Clinical pharmacokinetics. concepts and application*. Philadelphia: Lea and Febiger, 1980:97-108.
22. Irestedt L, Andreen M. Effects of neurolept anaesthesia on haemodynamics consumption in the dog with special reference to the liver and preportal tissues. *Acta Anaesthesiol Scand* 1979;23:1-12.
23. Hudson RJ, Stanski DR. Metabolism versus redistribution of fentanyl and alfentanil. *Anesthesiology* 1983;59:A243.

Effect of Etomidate on the Electroencephalogram of Patients with Epilepsy

Zeyd Y. Ebrahim, MD, Glenn E. DeBoer, MD, Hans Luders, MD, Joseph F. Hahn, MD, and Ronald P. Lesser, MD

EBRAHIM ZY, DEBOER GE, LUDERS H, HAHN JF, LESSER RP. Effect of etomidate on the electroencephalogram of patients with epilepsy. *Anesth Analg* 1986;65:1004-6.

Etomidate was given intravenously to 12 epileptic patients undergoing craniotomy for surgical removal of their seizure

focus. Electroencephalograms were recorded by means of subdural electrodes. Nine of the 12 patients showed an increase in epileptiform activity. In six of the nine patients, the activity was marked.

Key Words: ANESTHETICS, INTRAVENOUS—etomidate. COMPLICATIONS—epilepsy.

Etomidate (1,2) is a nonbarbiturate ultrashort-acting hypnotic that, because of its lack of cardiovascular side effects, has proven useful for the induction of anesthesia. Ghoneim and Yamada (3) have alluded to its use as an electroencephalogram (EEG) activator and advised against it in patients with epilepsy. We report here on the effect of etomidate on the EEG of patients with chronic epilepsy.

Methods

The research protocol was approved by the Institutional Review Board on Human Subjects Committee of the Cleveland Clinic, and informed consent was obtained from each patient, all of whom were to undergo cortical resection of their seizure focus. Twelve ASA Class I and II patients with intractable partial seizures (four men and eight women ranging in age between 16 and 39 yr) were studied. Each had two craniotomies, at the first of which subdural electrodes were inserted to define precisely the location of the epileptogenic focus and to evaluate the functional significance of the cortex underlying the subdural electrodes (4). This information was used by the surgeon to decide the extent of the cortical resection, which

was usually performed approximately 2 weeks later. Our studies were done during the first craniotomy.

The patients were premedicated with oral diazepam, 0.15 mg/kg, about 90 min prior to induction of anesthesia. On arrival in the operating room, 0.4 mg scopolamine was given intravenously (IV) and a #20 plastic catheter was placed in the radial artery. Anesthesia was induced with fentanyl, 10–12 μ g/kg, and thiopental, 3–5 mg/kg. Tracheal intubation was facilitated with pancuronium, 0.1 mg/kg. Anesthesia was maintained with 70% nitrous oxide in oxygen with pancuronium given as needed based upon responses to a nerve muscle stimulator. PaCO_2 was maintained between 27–30 torr and PaO_2 at about 100 torr. A frontotemporal craniotomy was performed, and a plate of subdural electrodes was placed. Nitrous oxide was then discontinued for 10 min, after which a 5 min baseline EEG was recorded. Next, etomidate, 0.2 mg/kg, was given and the EEG was recorded for an additional 5 min. These recordings were obtained approximately 3 hr after induction of anesthesia.

Results

Epileptiform activity increased in nine out of the 12 patients after the injection of etomidate (Table 1). The time interval between etomidate administration and patient awakening was approximately 90 min. All patients were fully conscious, without recall, and were not postictal on leaving the operating room. In the other three patients, no significant EEG changes were observed. The increased epileptiform activity was es-

Received from the Division of Anesthesiology, Department of Neurology, and the Department of Neurosurgery, The Cleveland Clinic Foundation, Cleveland, Ohio. Accepted for publication May 12, 1986.

Address correspondence to Dr. Ebrahim, Division of Anesthesiology, The Cleveland Clinic Foundation, 9500 Euclid Avenue, Cleveland, OH 44106.

Table 1. Epileptiform Activity in Patients after Injection of Etomidate

Patient number	A (Sharp waves/min before etomidate)	B (Sharp waves/min after etomidate)	Ratio B/A (Sharp waves/min after etomidate divided by sharp waves/min before etomidate)
1	12.8	23.4	1.83
2	5.1	29.1	5.71
3	5.0	19.3	3.86
4	1.2	28.0	23.33
5	0.4	2.0	5.00
6	0.0	1.0	1.00
7	0.0	0.0	0.0
8	86.9	86.9	1.00
9	0.0	16.2	16.2
10	0.6	10.6	17.67
11	0.6	84.6	141.0
12	13.0	120.0	9.23

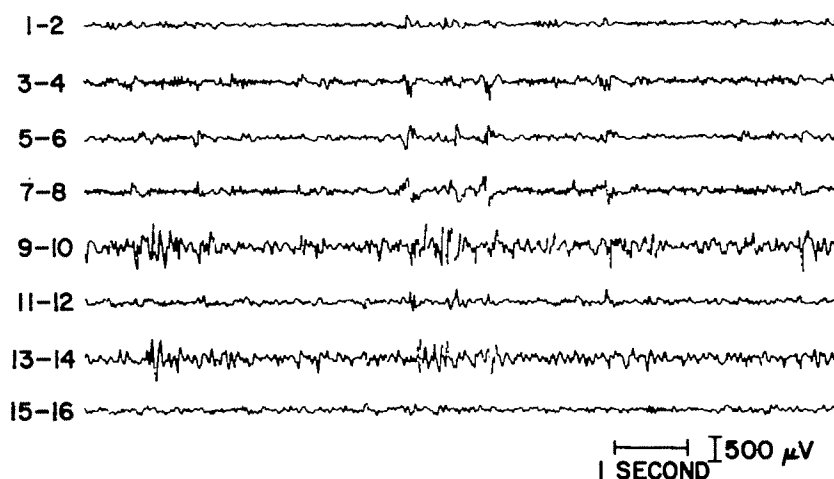


Figure 1. Before etomidate (electrocorticography from right basal temporal region).

pecially marked in six patients, recordings from one of whom are illustrated (Figs. 1,2).

Discussion

This study shows that etomidate increases epileptiform discharges in some but not all patients with epileptogenic abnormalities and confirms the observations of Ganchar et al. (5), who described activation of epileptogenic activity in two epileptics during electrocorticography preceding cortical resection. This study is also consistent with the description of epileptogenic activity in decerebrated cats after etomidate administration (6). Ghoneim and Yamada (3) reported in their study that 28% of the patients who received etomidate had violent myoclonic movements that, in 35% of these cases, resembled generalized convulsive seizures. They could not detect epileptiform discharges in the simultaneously recorded scalp

EEG, but because of the known association between myoclonus and epileptic seizures, they cautioned against the use of etomidate in epileptic patients. It is important to mention that etomidate is a powerful activator of β activity, which, together with muscle artifact, could obscure epileptogenic activity when recording from scalp electrodes. In addition, in scalp recordings, high amplitude β activity and epileptiform activity can look extremely similar, and therefore be difficult to distinguish.

The results reported here establish that etomidate like methohexital, is a hypnotic that not only has anesthetic properties but, paradoxically, in some patients also activates epileptogenic discharges and seizures. This last characteristic can be used advantageously during surgery for epilepsy when activation of spikes could possibly assist in defining potentially epileptogenic tissue in some patients. To define with more precision its usefulness under these conditions

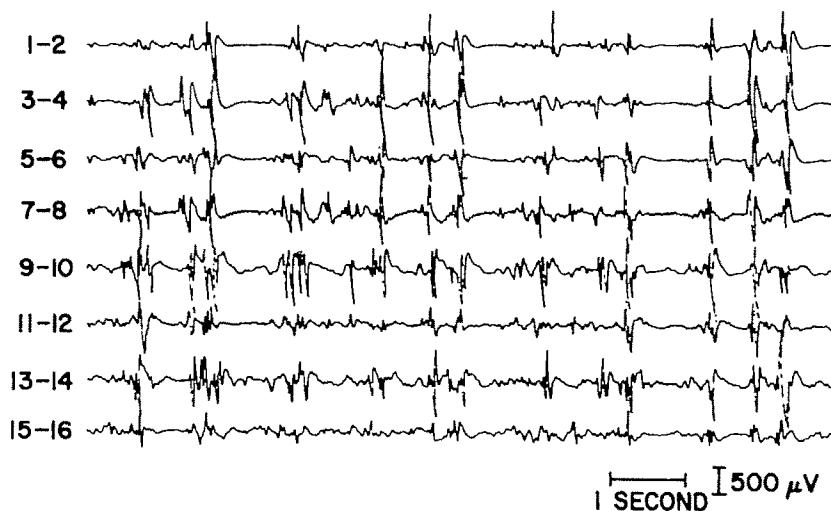


Figure 2. Three minutes after 13.5 mg etomidate (electrocorticography from right basal temporal region).

it would be necessary to establish further that etomidate activates epileptogenic cortex selectivity. In conclusion, considering the observation by Kreiger et al. (7) and our data, perhaps etomidate should be avoided in patients with epilepsy in the absence of further clinical studies.

References

1. Giese JL, Stanley TH. Etomidate: a new intravenous anesthetic induction agent. *Pharmacotherapy* 1983;3:251-8.
2. AMA Division of Drugs. *AMA drug evaluation*. 5th. ed. Chicago: American Medical Association 1983:409-10.
3. Ghoneim MM, Yamada T. Etomidate: a clinical and electroencephalographic comparison with thiopental. *Anesth Analg* 1977;56:479-85.
4. Hahn JF, Sellars M. Surgical techniques for relief from seizures. *The Cleveland Clinic Quarterly* 1984;51:307-11.
5. Ganchar S, Laxer KD, Kreiger W. Activation of epileptogenic activity by etomidate. *Anesthesiology* 1984;61:616-8.
6. Baiker-Heberlein M, et al. Investigations on the site of the central nervous action of the hypnotic agent etomidate in cats. (In German with English summary). *Anaesthetist* 1975;24:269-72.
7. Kreiger W, Copperman J, Laxer KD. Seizures with etomidate anesthesia. *Anesth Analg* 1985;64:1226-7.

Maternal Cortical Vein Thrombosis and the Obstetric Anesthesiologist

Dirk Younker, MD, Monica M. Jones, MD, Jayshree Adenwala, MD, Alan Citrin, MD, and Thomas H. Joyce III, MD

YOUNKER D, JONES MM, ADENWALA J, CITRIN A, JOYCE TH III. Maternal cortical vein thrombosis and the obstetric anesthesiologist. *Anesth Analg* 1986;65:1007-12.

Maternal cortical vein thrombosis is a potentially fatal complication of pregnancy and the puerperium. Patients may present with focal neurologic deficits, seizures, or symptoms indicating increased intracranial pressure. Associated conditions include maternal dehydration and preeclampsia or frank eclampsia. Parturients may require anesthesia for various

types of delivery. Safe administration of appropriate anesthesia must take into account the possible presence of a coagulopathy or reduced intracranial compliance. Case presentations, a literature review, possible pathogenetic mechanisms, and specific anesthetic considerations are discussed to enable the obstetric anesthesiologist to develop a rational plan of management.

Key Words: ANESTHETICS, OBSTETRIC. PREGNANCY—coronary vein thrombosis. BRAIN—coronary vein thrombosis.

For more than 100 years clinicians have recognized the neurologic syndromes produced by maternal cortical vein thrombosis (CVT) (1) as well as its tendency to occur during pregnancy and the puerperium (2). The signs and symptoms of CVT are caused by thrombotic obstruction of the superior longitudinal sinus or of the cortical veins, which produces impaired cerebrospinal fluid absorption and increased intracranial pressure followed by headache, nausea, and coma (3,4). In addition, blockade of the draining cortical veins with subsequent regional cerebral infarction may produce focal neurologic signs or seizures (4,5). Even though the morbidity and mortality of CVT approach 30% (6,7), the antemortem diagnosis of CVT remains elusive. Cortical vein thrombosis is most often mistaken for eclampsia or aneurysmal rupture (8,9); indeed, the obstetric anesthesiologist may encounter this potentially fatal disorder for the first time when asked to anesthetize a neurologically unstable parturient who is presumed to be eclamptic and who requires an abdominal delivery.

In the course of 24,000 consecutive deliveries performed over 15 months at Jefferson Davis Hospital in Houston, Texas, four cases of suspected CVT were

confirmed through radiography. Three of these four cases are presented below to illustrate its various mode of presentation (see Table 1). A discussion of the etiology of CVT and suggestions for the anesthetic management of parturients with CVT are offered.

Case Presentations

Patient 1

A 20-yr-old gravida 1, para 0, abortus 0 patient in her fortieth week of gestation arrived at the labor suite for delivery. Her medical history included poliomyelitis as a child. Physical examination revealed a mild right-sided lower extremity weakness that had been unchanged for many years. Other medical history was noncontributory. Vital signs and admission laboratory values were within normal limits.

After two failed attempts at epidural catheter placement (both resulting in accidental dural punctures) the patient was given ketamine (total dose 50 mg) and diazepam (total dose 10 mg) intravenously for vaginal forceps delivery and a prolonged perineal repair. Her infant's Apgar scores were 8 at 1 min and 9 at 5 min.

A severe frontal headache developed shortly after delivery. Headache, nausea, and vomiting continued with varying severity for the next 6 days despite placement of a sterile epidural blood patch with 10 ml of autologous blood on the day after delivery. At the time of discharge 5 days later the patient complained only

Received from the Department of Anesthesiology, Baylor College of Medicine, Houston, Texas. Accepted for publication May 5, 1986.

Address correspondence to Dr. Younker, Assistant Professor, Department of Anesthesiology, Baylor College of Medicine, One Baylor Plaza, Houston, TX 77030.

Table 1. Characteristics of Patients with Cortical Vein Thrombosis

	Patient		
	1	2	3
Admission diagnosis	Intrauterine pregnancy	Eclampsia	Pregnancy-induced hypertension
Age	20	15	18
Parity	Gravida 1, para 0	Gravida 1, para 0	Gravida 1, para 0
Weeks of gestation	40	38	43+
Medical history	Polio myelitis (poorly documented) mild right hemiparesis	Negative	Negative
Prior medication	None	None	None
Allergies	Penn G	None	None
Family history	None	None	None
Onset of symptoms	Fever, headache, weakness	Seizures, fever	Seizures, disseminated intravascular coagulation
Mode of delivery	Vaginal forceps	Cesarean section	Cesarean section
Anesthetic	Lumbar epidural; dural puncture \times 2	General endotracheal	General endotracheal
Apgar scores	8/9	7/9	7/8
Clinical	Seizures, hemiparesis, aphasia	Hypertension, seizures	Seizures, coagulopathy, hypertension
Radiologic findings	Cerebral arteriogram: positive	CAT scan: positive	CAT scan: positive
Urinalysis	2+ bacteria	1+ protein	2+ protein
Outcome	Return to baseline neurologic status	Complete resolution	Complete resolution
Discharge diagnosis	Cerebral venous thrombosis	Cerebral venous thrombosis; eclampsia	Cerebral venous thrombosis

of a mild headache when erect. At home the morning after discharge the patient awoke diaphoretic, with an intense throbbing headache and severe motor weakness of both her right-sided extremities. On admission to the emergency department the patient had a temperature of 40°C. Initial laboratory studies showed only an abnormal plasma lactate dehydrogenase level of 239 IU/L. Cerebrospinal fluid was xanthochromic with a 60 mg/dl glucose concentration and total protein content of 207 mg/dl. No organisms were seen on Gram's stain of the spinal fluid.

A computed axial tomography (CAT) scan of her head, a myelogram, and chest x-rays were all normal. Cultures of blood, sputum, and cerebrospinal fluid were all sterile. In the following days the patient's neurologic state deteriorated to a complete right-sided hemiparesis, an expressive aphasia, and an episode of generalized seizure activity. Cerebral arteriograms revealed a superior sagittal sinus thrombosis with a mass effect producing compression of the left Sylvian vessels (Fig. 1). Remarkably, her neurologic signs spontaneously improved with complete resolution of her aphasia and minimal residual right lower extremity weakness.

Shortly thereafter, the patient developed multiple pulmonary emboli verified by ventilation perfusion scanning. These cleared after anticoagulant therapy. She was discharged 6 weeks after her original admission with mild motor deficits indistinguishable from her normal neurologic status.

Patient 2

A 15-yr-old gravida 1, para 0, abortus 0 patient at 38 weeks of gestation was brought to the labor suite after having suffered a grand mal seizure at home. Physical examination was remarkable for her obvious postictal state. Deep tendon reflexes were slightly more brisk than normal, and the patient appeared moderately dehydrated. Urinalysis revealed 1+ protein. All other laboratory data at the time of admission, including prothrombin time, partial thromboplastin time, and fibrinogen level, were normal. The patient's medical history and familial history were noncontributory. Blood pressure initially was 140/95 mm Hg and her oral temperature was 38°C. Plasma colloid osmotic pressure was elevated to 22 mm Hg (normal range 17–20 mm Hg). Treatment was initiated with fluids, phenytoin sodium, and magnesium sulfate. However, the patient's blood pressure increased on the night of admission to 200/110 mm Hg and repetitive seizure activity occurred. An urgent cesarean section was performed under general endotracheal anesthesia. The technique employed consisted of a rapid sequence induction using cricoid pressure, 3 mg intravenous *d*-tubocurarine, 200 mg intravenous thiopental, and 100 mg intravenous succinylcholine. Anesthesia was maintained with nitrous oxide-oxygen in a ratio of 4:4 L/min. Halothane (0.5%) was added to the inspired mixture. Muscle relaxation was produced with an intravenous infusion of 0.2% suc-



Figure 1. Delayed venous phase cerebral arteriogram of patient 1. Extrinsic compression of the Sylvian vessels by cortical vein thrombosis is apparent at the upper right.

cynylcholine. Her infant's Apgar scores were 7 at 1 min and 9 at 5 min.

Repetitive, generalized seizure activity continued for 24 hr postoperatively. A CAT scan of the head revealed right hemispheric cortical venous thrombosis. Seizure activity abated within 48 hr, with therapy consisting of hydration, phenytoin sodium, magnesium sulfate, and packed red cell transfusions. A subsequent CAT scan revealed complete clearing of the thrombosis. The patient was discharged shortly thereafter with a normal neurologic examination.

Patient 3

An 18-yr-old gravida 1, para 0, abortus 0 patient at 43 weeks gestation was found to have diastolic hypertension during a clinic visit. Initial physical evaluation revealed a diastolic blood pressure of 110 mm Hg, deep tendon reflexes that were mildly hyperreflexic and the presence of mild pedal edema. Urinalysis revealed 2+ proteinuria. The patient complained of seeing spots before her eyes. Medical history was noncontributory. She was given magnesium sulfate therapy and induction of labor with oxytocin was attempted. However, severe, abrupt increases in maternal blood pressure and late decelerations in fetal heart rate necessitated urgent cesarean section under general endotracheal anesthesia. A rapid sequence induction was performed using cricoid pressure, 3 mg

intravenous (IV) *d*-tubocurarine, 200 mg IV thiopental, and 100 mg intravenous succinylcholine. Anesthesia was maintained with nitrous oxide-oxygen 4:4 L/min with 0.5% halothane. Muscle relaxation was provided by a continuous infusion of 0.2% succinylcholine. Her infant's Apgar scores were 7 at 1 min and 8 at 5 min. The operation was complicated by continuous blood loss requiring multiple transfusions of packed red blood cells, platelets, fresh frozen plasma, and cryoprecipitate. In the immediate postoperative period, the patient suffered a gastrointestinal hemorrhage and developed generalized recurrent seizure activity. A CAT scan revealed a superior sagittal sinus thrombosis. The coagulopathy slowly resolved and her seizure activity ceased. She was discharged to her home with a normal neurologic examination.

Discussion

Cortical vein thrombosis has been the subject of an exhaustive monograph by Kalbag and Woolf (8). In addition, at least four extensive series discussing CVT in the puerperium have appeared in the past 20 years (6,7,9,10). However, although the clinical presentation of CVT has become more widely recognized, its pathogenesis remains a matter of conjecture.

Kendall (11) was among the first to suggest that the etiology of puerperal CVT might be found by con-

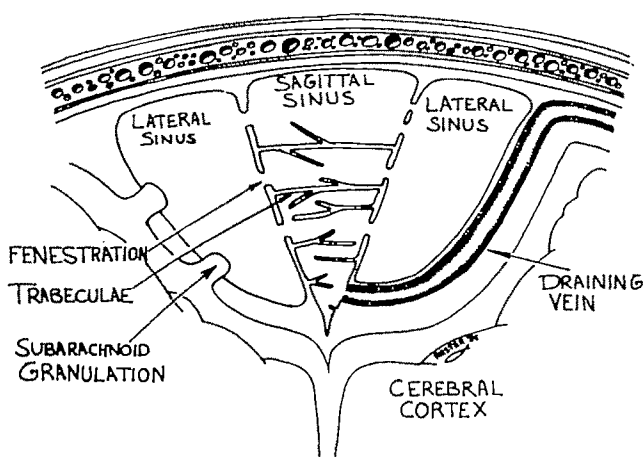


Figure 2. Coronal view of the structures within the superior sagittal sinus with its draining cortical veins. Artist's interpretation.

sidering those aspects of the disorder that produce Virchow's classic triad: 1) stasis of blood flow; 2) vascular endothelial damage; and 3) a hypercoagulable state. If a careful search is made, each of these conditions for the generation of thrombosis may exist in the pregnant patient, in particular one who presents with toxemia or dehydration.

1. Stasis of intracerebral blood flow. The longitudinal sinus itself is a valveless, low pressure structure with a triangular cross-section (5). Trabeculae may cross it, and it may be divided horizontally by a continuous membrane (12,13) (Fig. 2). Also, the longitudinal sinus receives the cerebral veins at its inferior angle, which is acute. The veins have thin walls, few muscle fibers, and no valves, thereby permitting reversal of the direction of blood flow when the sinus into which they normally drain is occluded (8, pp 25-26). These anatomic factors predispose to turbulent flow and even stasis, but by themselves cannot initiate thrombus formation.
2. Damage of intracerebral vessels. Traumatic damage to the endothelial lining of cortical sinuses and veins must occur, as well as the element of stasis, in order to produce the appropriate conditions for formation of a thrombus. Clearly such elements may operate during labor, especially throughout the second stage. During this period, extreme changes in intraabdominal pressure, such as those caused by maternal anxiety or bearing-down efforts, may be rapidly transmitted to the subarachnoid space (14-16). The source of the transmitted pressure change is thought to lie in the impingement either of spinal nerves or of an engorged vertebral plexus upon external evaginations of the

dura around the spinal nerves. Even a small increase in intraabdominal pressure may cause a precipitous and parallel increase in cerebrospinal fluid pressure because of the incompressibility of this fluid column (17). Kendall (11) believed that the violent fluctuations in pressure so generated might be sufficient to damage the endothelium of the fragile intracranial sinuses and veins.

3. Hypercoagulable state. It has been known for many years that important alterations tending to make blood more coagulable are present during pregnancy and the puerperium. The number of platelets is increased by about 30% after parturition (18), and the increase may even be higher after postpartum hemorrhage (19). In addition to an increased number of platelets, blood elements newly formed by a reactive bone marrow may exhibit increased adhesiveness (20). Also, the fibrinogen content of the blood is increased, as reflected by an increase in the erythrocyte sedimentation rate (21). Placental thromboplastin may be released into the circulation after manual extraction of the placenta (22), with initiation of the clotting cascade. Also, antithrombin III levels are known to be depressed in preeclamptic patients (23), and it is these patients who may be at high risk for development of CVT. Additionally, after the discovery of the role arachidonic acid metabolites play in the interaction between platelets and vascular endothelium (24,25), attention has shifted to changes in their respective activities during pregnancy. Preliminary studies indicate that, during late pregnancy and the puerperium, platelets are hyperaggregable in spite of grossly elevated levels of plasma prostacyclin (26). Finally, it would appear that during this period both thromboxane A_2 plasma levels and the release of thromboxane A_2 in response to thrombin-induced platelet aggregation are enhanced (27).

It is interesting to note that these hemostatic abnormalities are present at the same time during which the peak incidence of pulmonary thromboembolism and CVT occurs. Because pulmonary thromboembolism and CVT frequently occur in the same patient (4; 8, pp 158-159) it is tempting to speculate that these may be discrete manifestations of a global hypercoagulable state involving an imbalance between circulating levels of prostacyclin and thromboxane A_2 . The finding of decreased levels of plasma prostacyclin in preeclampsia is of particular interest in this respect (28,29). The abnormally low levels of prostacyclin may encourage the formation of platelet aggregates in areas of stasis or vascular damage. Indeed, the propensity of preeclamptic patients to develop deep venous

thrombosis, pulmonary thromboembolism, or CVT is supported by general clinical experience.

The patients described above demonstrate the variations in clinical presentation of CVT during pregnancy and the puerperium. The last two patients are of particular interest because CVT before parturition is thought to be rare (4,6-8,10). In patients such as these, it cannot be assumed that the endothelium of the intracranial vessels has been damaged during labor through the mechanism cited above. Therefore, other factors must be operative to promote thrombus formation at this time. What such factors may be remains unknown.

Published data place the incidence of CVT between 1 in 10,000 pregnancies and 1 in 600,000 consecutive deliveries (30). However, these statistics are difficult to evaluate, because cases are often not documented by radiographic or autopsy findings. In addition, the incidence of subclinical cases of CVT that remain unrecognized because of lack of characteristic signs and symptoms may be greater than commonly recognized (5). Certain series indicate an occurrence of clinical CVT between 1 in 1666 pregnancies and 1 in 3000 pregnancies (6,7,10). The four radiographically proven cases in 24,000 consecutive deliveries at Jefferson Davis Hospital, three of which are presented in detail in the present paper, reveal an incidence of 1 in 6,000 consecutive pregnancies. These data suggest that the true incidence of CVT may be more frequent than is generally assumed. Thus, the obstetric anesthesiologist should give the diagnosis of CVT particular attention when evaluating the neurologic examination of a parturient who has convulsed or who has a history suggestive of intracranial hypertension.

The anesthetic management of patients with CVT presents challenges, especially those cases in which maternal or fetal deterioration necessitates urgent abdominal delivery. The anesthetic technique should be individually modified to meet the combined needs of an endangered fetus and a mother who may be frankly eclamptic. The constraints imposed by the presence of elevated intracranial pressure or a coagulopathy must also be considered. The existence of a coagulopathy contraindicates the use of regional anesthesia for labor or delivery. The presence of intracranial hypertension may also argue against the use of regional anesthesia, because a precipitous decrease in systemic pressure may reduce cerebral perfusion pressure below the critical level necessary to perfuse ischemic brain tissue. Also, in the presence of an asymmetric mass lesion such as an intracerebral hematoma, cerebrospinal fluid leakage through an unintentional dural puncture may result in brainstem herniation. On the other hand, carefully instituted lumbar epidural anes-

thesia may be therapeutic because it will abolish the abrupt increases in cerebrospinal fluid pressure associated with maternal expulsive efforts. If general anesthesia is thought appropriate, rapid sequence induction with maintenance of cricoid pressure is mandatory. Ketamine should be avoided. Adequate muscle relaxation, as indicated by peripheral nerve stimulation, should be present prior to intubation to prevent coughing or straining on the endotracheal tube. The use of intravenous lidocaine or trimethaphan camsylate prior to induction may blunt the hypertensive response to intubation. Low concentrations of an inhalational anesthetic agent will decrease maternal awareness without adverse effect on the fetus (31). Isoflurane may be the best choice in this respect because intracranial pressure remains stable at concentrations of less than 1% (32) and isoflurane does not enhance cerebrospinal fluid production (33). Thus, with isoflurane there is a greater likelihood that intracranial pressure relationships will remain unchanged. Finally, repeated and thorough postpartum neurologic examinations may detect subtle shifts in clinical signs that will herald the onset of decompensation produced by a rapidly expanding intracranial hematoma.

References

1. Gowers WR. Diagnosis of diseases of the brain and spinal cord. New York: William Wood and Co., 1885:166-8.
2. Abercrombie J. Pathological and practical researches on diseases of the brain and spinal cord. 3rd ed. Philadelphia: Carey, Lea, and Blanchard, 1836:67-8.
3. Symonds CP. Hydrocephalic and focal cerebral symptoms in relation to thrombophlebitis of the dural sinuses and cerebral veins. *Brain* 1937;60:531-50.
4. Dubois J. Les thrombophlébites cérébrales du post-partum. *Gynec et Obstet* 1956;55:472-93.
5. Martin JP. Thrombosis in the superior longitudinal sinus following childbirth. *Br Med J* 1941;2:537-40.
6. Carroll JD, Leak D, Lee H. Cerebral thrombophlebitis in pregnancy and the puerperium. *Q J Med* 1966;35:347-68.
7. Cross JN, Castro PO, Jennett WB. Cerebral strokes associated with pregnancy and the puerperium. *Br Med J* 1968;3:214-8.
8. Kalbag RM, Woolf AL. Cerebral venous thrombosis. London: Oxford University Press, 1967.
9. Koller TH, Stamm H, Hauser GA, Klinger M. Die zerebralen Venen-und Sinusthrombosen in der Geburtshilfe. *Thrombos Diathes Haemorrh* 1957(Stutt.):1:37-54.
10. Srinivasan K. Cerebral venous and arterial thrombosis in pregnancy and puerperium: a study of 135 patients. *Angiology* 1983;34:731-46.
11. Kendall D. Thrombosis of intracranial veins. *Brain* 1948;71:391-8.
12. O'Connell JEA. Some observations on the cerebral veins. *Brain* 1934;57:484-503.
13. Browder J, Browder A, Kaplan HA. The venous sinuses of the cerebral dura mater: I. Anatomical structures within the superior sagittal sinus. *Arch Neurol* 1972;26:175-80.

14. McCausland AM, Holmes F. Spinal fluid pressures during labor: preliminary report. *West J Surg Obstet Gynec* 1957;65:220.
15. Marx GF, Oka Y, Orkin LR. Cerebrospinal fluid pressures during labor. *Am J Obstet Gynec* 1962;84:213-9.
16. Alman RW, Fazekas JF. Cerebral physiology of the augmented Valsalva maneuver. *Am J Med Sci* 1962;244:202-9.
17. Hamilton WF, Woodbury RA, Harper HJ Jr. Physiologic relationships between intrathoracic, intraspinal and arterial pressures. *JAMA* 1936;107:853.
18. Dawbarn RY, Earlam F, Evans WH. The relation of blood platelets to thrombosis after operation and parturition. *J Path Bact* 1928;31:833-73.
19. Bland PB, Goldstein L. Coagulability of blood in pregnancy. *Am J Obstet Gynec* 1932;23:815-21.
20. Gilligan DR, Ernstene AC. Relationship between erythrocyte sedimentation rate and fibrinogen content of plasma. *Am J Med Sci* 1934;187:552-6.
21. Wright HP. Changes in adhesiveness of platelets following parturition and surgical procedures. *J Path Bact* 1942;54:461-8.
22. Jurgens J, Stein F. Intravasale Gerinnung als koagulopatisches Syndrom nach manueller Losung der Placenta. *Schweiz Med Wschr* 1954;84(i):346-51.
23. Weenink GH, Borm JJJ, Ten Cate JW, Treffers PE. Antithrombin III levels in normotensive and hypertensive pregnancy. *Gynecol Obstet Invest* 1983;16:230-42.
24. Moncada S, Vane JR. Arachidonic acid metabolites and the interactions between platelets and blood vessel walls. *N Engl J Med* 1979;300:1142-47.
25. Ubatuba FB, Moncada S, Vane JR. The effect of prostacyclin (PGI₂) on platelet behavior, thrombus formation in vivo and bleeding time. *Thrombos Haemost* (Stutt) 1979;41:425.
26. Lewis PJ, Boylan P, Friedman LA, Hemsby CN, Downing I. Prostacyclin in pregnancy. *Br Med J* 1980;280(2):1581-2.
27. Ylikorkala O, Viinikka L. Thromboxane A₂ in pregnancy and the puerperium. *Br Med J* 1980;280:1601.
28. Remuzzi G, Marchesi D, Zoja C, Muratore D, Mecca G, Mistrani R, Rossi E, Barbato M et al. Reduced umbilical and placental vascular prostacyclin in severe pre-eclampsia. *Prostaglandins* 1980;20:105-10.
29. Goodman RP, Killam AP, Brash AR, Brauch RA. Prostacyclin production during pregnancy: comparison of production during normal pregnancy and pregnancy complicated by hypertension. *Am J Obstet Gynec* 1982;142:817-22.
30. Burroughs GN, Ferris TG. Medical complications during pregnancy. Philadelphia: WB Saunders and Co., 1982:451.
31. Warren TM, Datta S, Ostheimer GO, Naulty JS, Weiss JB, Morrison JA. Comparison of maternal and neonatal effects of halothane, enflurane and isoflurane for cesarean delivery. *Anesth Analg* 1983;62:516-20.
32. Adams RW, Cucchiara RF, Gronert GA, Messick JM, Michenfelder JD. Isoflurane and cerebrospinal fluid pressure in neurosurgical patients. *Anesthesiology* 1981;54:97-9.
33. Artru AA. Isoflurane does not increase the rate of CSF production in the dog. *Anesthesiology* 1984;60:193-7.

Continuous Noninvasive Monitoring of Cardiac Output with Esophageal Doppler Ultrasound during Cardiac Surgery

Jonathan B. Mark, MD, Richard A. Steinbrook, MD, Laverne D. Gugino, MD, PhD, Rosemarie Maddi, MD, Barbara Hartwell, MD, Richard Shemin, MD, Verdi DiSesa, MD, and Wasima N. Rida, MS

MARK JB, STEINBROOK RA, GUGINO LD, MADDI R, HARTWELL B, SHEMIN R, DISESA V, RIDA WN. Continuous noninvasive monitoring of cardiac output with esophageal Doppler ultrasound during cardiac surgery. *Anesth Analg* 1986;65:1013-20.

Esophageal Doppler ultrasonography offers a continuous and noninvasive alternative to standard thermodilution cardiac output monitoring. A total of 372 simultaneous measurements of Doppler and thermodilution cardiac output were compared in 16 patients undergoing cardiac surgery. In addition, echocardiographic aortic diameter measurement, necessary for Doppler calibration, was compared with direct surgical measurement in 23 patients. Echocardiographic aortic measurement was often time consuming and

correlated poorly ($r = 0.31$) with surgical measurement. On the other hand, Doppler cardiac output was determined easily and accurately tracked thermodilution cardiac output ($R^2 = 0.95$, common slope coefficient 1.050, by multiple linear regression). Furthermore, Doppler cardiac output was more reproducible, showing less short-term variability than thermodilution cardiac output. The esophageal Doppler technique allows cardiac output monitoring in patients for whom invasive monitoring is not warranted.

Key Words: MONITORING, CARDIAC OUTPUT—Doppler ultrasonography. MEASUREMENT TECHNIQUES, CARDIAC OUTPUT—Doppler ultrasonography.

Optimal monitoring during general anesthesia focuses upon techniques that provide on-line or near-continuous information regarding physiological status with minimal cost, discomfort, or associated risk. Routine monitoring of circulatory function under anesthesia generally has been limited to heart rate, blood pressure, and electrocardiography. Cardiac output (CO) determination has been reserved for patients with severe circulatory derangement or those undergoing major surgery, because the standard technique of thermodilution flow measurement requires right heart catheterization with its attendant costs and risks (1-3). Furthermore, thermodilution

cardiac output (TDCO) measurement is just that, a measurement, because it requires repeated injections by the operator, and can only provide intermittent information at best. An alternative means of monitoring CO would seem desirable.

Doppler ultrasonography is a noninvasive alternative that has been shown to correlate well with TDCO measurement (4-7). Early techniques of Doppler CO measurement required repeated placement of a suprasternal Doppler probe for serial measurements. The development of this measurement technique into a practical monitoring mode has now become possible with the incorporation of the Doppler ultrasonic probe into a standard esophageal stethoscope. This report describes our experience with this device in patients undergoing cardiac surgery. The primary purpose of this study was to compare this Doppler technique of CO measurement with the standard thermodilution technique. In addition, because an accurate echocardiographic measurement of aortic diameter is an important component of this noninvasive CO technique, we attempted to validate ultrasound aortic diameter measurement with direct surgical measurement.

This study was supported in part by NIH #R44 HL3192002 and presented in part at the Annual Meeting of the Society of Cardiovascular Anesthesiologists, Montreal, Canada, April 1986.

Received from the Departments of Anesthesia and Surgery, Brigham and Women's Hospital, Harvard Medical School, Boston, Massachusetts, and the School of Public Health and Community Medicine, Department of Biostatistics, University of Washington, Seattle, Washington. Accepted for publication May 12, 1986.

Address correspondence to Dr. Mark, Department of Anesthesia Brigham and Women's Hospital 75 Francis Street Boston, MA 02115.

Methods

Ultrasonography Principles and Techniques

Ultrasonic monitoring of blood flow velocity, stroke volume (SV), and CO have been described in detail in recent clinical reports (6,7). In brief, when an ultrasound beam is directed at a column of flowing blood, the reflected sound wave will have a shift in frequency. The magnitude of this Doppler shift is directly proportional to the velocity of blood flow. Stroke volume can be calculated by multiplying this average blood velocity during a systolic cycle, by ejection time, and by the cross-sectional area through which the blood flows (the aorta). Knowledge of the heart rate then allows determination of CO. A complete description of these techniques and the underlying assumptions is available for the interested reader (6,8,9).

The device utilized in the present investigation was a commercially available instrument (Ultracom®, Lawrence Medical Systems), modified to accept input from an esophageal Doppler probe. Three steps are required to initiate continuous monitoring of CO (Fig. 1). The first is a measurement of ascending aortic diameter. The second involves the placement of an esophageal Doppler transducer to track descending aortic flow. The final step involves the one time measurement of ascending aortic flow via Doppler ultrasound from the suprasternal notch (SSN) and calibrating the esophageal transducer to this measured value of left heart output. These procedures are described in greater detail in the following paragraphs.

A precordial transducer was used to measure the internal diameter of the ascending aorta just above the sinuses of Valsalva, via pulsed A-mode echocardiography. The instrument used this measurement to compute aortic cross-sectional area, assuming circular aortic geometry. Patients with aortic valve disease were excluded from evaluation. This aortic diameter measurement was always made in the preoperative holding area and required between 5 and 30 min, depending upon ease of measurement, operator experience, and whether more than one operator made measurements.

The second step, performed in the operating room after induction of anesthesia and tracheal intubation, involved placement of a 24-F esophageal stethoscope containing a 6-mm continuous wave Doppler (CWD) piezoelectric transducer at its tip. The stethoscope also allowed auscultation of heart and breath sounds, as well as temperature measurement. This transducer was positioned to maximize an audible signal, which coincided with a maximal signal level on a digital display. This assured the operator that the transducer

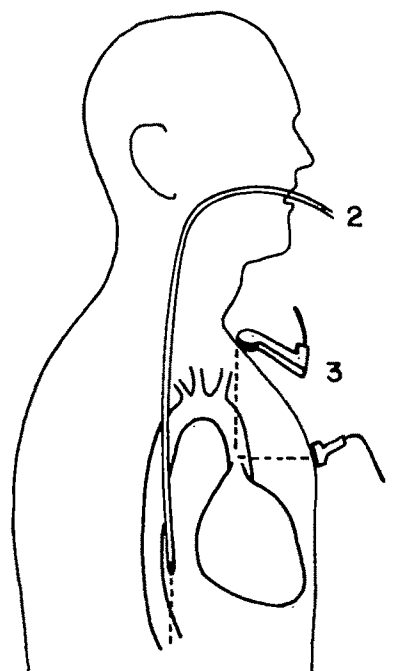


Figure 1. Schematic representation of the three steps involved in esophageal Doppler cardiac output monitoring. See Methods for details.

was properly directed at flow in the descending thoracic aorta. The manipulation required 2–10 min and occurred during bladder catheterization and lower extremity surgical preparation.

The third and final step involved measurement of ascending aortic blood flow velocity by an additional CWD transducer placed in the SSN. This systolic flow velocity was automatically multiplied by the aortic cross-sectional area computed by the instrument in step one above. This calculation provided an absolute flow measurement, i.e., CO. The monitor screen revealed the relative SV of each left ventricular ejection, marching along in real time. Twelve consecutive beats were averaged to calculate CO. The monitor updated its digital display of CO with each subsequent collection of twelve new beats. The monitor also displayed digital values of ejection time and signal level, helping the operator to be certain that a good measurement of CO had been made from the SSN. By pressing a switch, the esophageal probe was calibrated to continuously monitor the flow in the descending aorta. The SSN probe was removed after this calibration procedure, and the surgical chest preparation for cardiac surgery was completed. This final SSN/esophageal calibration step required 2–10 min.

To summarize, this technique involves following flow in the descending aorta via transesophageal ultrasonography, having calibrated this flow to total

Table 1. Demographic Profile

	Age (yr)	Weight (kg)	Height (cm)	Sex (M/F)	Procedure
Aortic comparison study (<i>n</i> = 23)	56 ± 10 (34-75)	80 ± 13 (61-110)	172 ± 11 (152-198)	21/2	23 CABG
Cardiac output comparison study (<i>n</i> = 16)	60 ± 10 (39-75)	75 ± 13 (60-102)	170 ± 8 (152-180)	11/5	6 CABG, 6 REOP CABG, 2 REOP MVR, 1 CABG-MVA, 1 CABG-CAROTID

Values are mean ± SD. Values in parentheses are ranges.

Abbreviations: CABG, coronary artery bypass grafting; REOP = repeat operation; MVR, mitral valve replacement; MVA, mitral valve annuloplasty; CAROTID, carotid endarterectomy.

systemic output or ascending aortic flow. The ascending aortic flow is a composite of two measurements, the ascending aortic diameter and SSN velocity measurements.

Thermodilution Technique (TDCO)

TDCO was measured in patients with 7-F pulmonary artery (PA) catheters in place (American Edwards). Thermal indicator was a 10-ml injection of iced (0-5°C) 5% dextrose solution. The injection was made in less than 4 sec, always at sustained end-expiration. The American Edwards COM-1® cardiac output computer was used in all studies.

When TDCO was compared with simultaneous esophageal Doppler cardiac output (ECO), measurements were repeated up to five times as rapidly as possible to define an epoch. Isolated single measurements of TDCO (or ECO) were never accepted for analysis.

Surgical Aortic Measurement

In another group of 23 patients, ultrasound aortic measurement (UC-AO) was compared to a surgical aortic measurement (SURG-AO) carried out as described below. Before institution of cardiopulmonary bypass, the supracoronary ascending aorta was isolated by dissection through the aortopulmonary pericardial reflection. A large silk ligature was passed around the aorta and used to measure its circumference to the nearest millimeter. Aortic wall thickness was initially measured from the aortic button removed for implantation of the proximal saphenous vein anastomosis. Because this wall thickness was difficult to determine precisely (because of maceration of the specimen, variability in aortic fat and resolution of measurement devices), a standard value of 2 mm for aortic wall thickness was adopted and used for all calculations. Surgical aortic diameter was then calculated using a standard algebraic formula, and this value was compared with the UC-AO.

Patient Population

Informed consent was obtained from all patients enrolled in this study, in accordance with the Hospital's Human Studies Committee. After we had gained clinical experience with the ultrasound monitor, 23 patients were enlisted in the aortic measurement phase of the study, 16 participated in the TDCO/ECO comparison study, and four were enlisted in both studies. The demographic profiles of the patients are summarized in Table 1.

In each patient, UC-AO was determined preoperatively while the intravascular catheters were being placed by the anesthesia team. When more than one investigator was available, UC-AO was determined by two or three observers and an average value taken. The UC-AO was then used for the surgical aortic comparison study, or as the entered value for the thermodilution output comparison.

Subsequently, the 16 patients in the TDCO/ECO study were anesthetized and ECO monitoring established as described above. During the course of anesthesia and surgery, pairs of simultaneous TDCO and ECO values were recorded.

Statistical Analysis

Comparison of simultaneous TDCO and ECO epochs was undertaken by first calculating the mean TDCO and mean ECO for each epoch, then using these epoch averages in simple linear regression (SLR) and multiple linear regression (MLR) analyses. The two-sample T^2 statistic and Cook's distance (10,11) were used to define exclusion criteria for one TDCO/ECO outlier. To assess the short-term variability in TDCO and ECO, the within-epoch variabilities of each were computed. Subsequently, the within-epoch variability of TDCO was compared to the within-epoch variability of ECO by a paired Student's *t*-test. Simple linear regression also was utilized to examine the relationship between SURG-AO and UC-AO. A value of $P < 0.05$ was considered statistically significant.

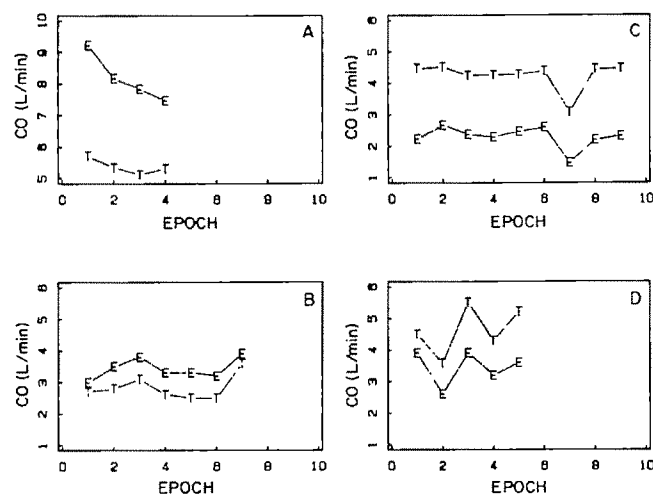


Figure 2. Thermodilution cardiac output (T) and esophageal Doppler cardiac output (E) values for each epoch recorded in four different patients. Note that in (A) and (B), E overestimates T, whereas in (C) and (D), E underestimates T. CO, cardiac output.

Results

Cardiac Output Measurement: Ultrasound/Thermodilution Comparison

A total of 372 paired measurements of CO by esophageal Doppler and by thermodilution were made in 16 patients. CO determinations were divided into 113 epochs; each epoch consisted of between 2 and 5 pairs of values obtained during a hemodynamically stable period of less than 5 min. The values of ECO ranged from 1.5–13.1 L/min, whereas TDCO ranged from 2.5–6.9 L/min.

One outlier (ECO 13.1, TDCO 6.9) that was well outside the region of the rest of the data was removed from the data analysis. A two-sample T^2 statistic measuring the distance of this point from the center of the remaining data was 29.574 ($P < 0.001$; a large value for this test statistic supports our observation of an outlier). This data point also significantly affected the values of the parameter estimates in the SLR and MLR analyses. Its Cook's distance (which measures the impact a single data point has on the values of these parameter estimates) was the largest of all the data points and was an order of magnitude greater than for any other data point. We were left with 112 epochs (ranges of ECO, 1.5–9.2 L/min; TDCO 2.5–6.3 L/min).

Inspection of epoch by epoch TDCO/ECO plots for each individual patient revealed a fairly constant calibration error between TDCO and ECO across time. Figure 2 clearly demonstrates these calibration errors, with ECO either consistently overestimating or consistently underestimating TDCO in a given patient.

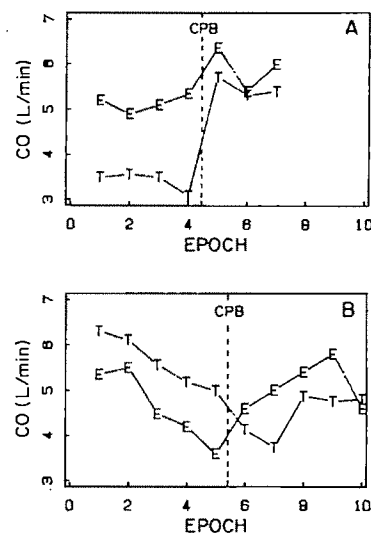


Figure 3. Effect of cardiopulmonary bypass upon thermodilution cardiac output (T)/esophageal Doppler cardiac output (E) relationship. The calibration error between T and E is changed after the fourth epoch in (A) and after the fifth epoch in (B). In each case, the subsequent epochs were measured after bypass. CO, cardiac output; CPB, cardiopulmonary bypass.

Because each patient displayed his/her own calibration error, it is inappropriate to fit one straight line through the combined data of the 16 patients as is done with SLR. An appropriate model fits a separate regression line through each patient's data, but constrains the slopes of these separate lines to be identical. This was accomplished with multiple regression analysis. If ECO is tracking TDCO well, the common slope coefficient should be close to one and each patient's intercept reflects his/her calibration error. A patient's estimated intercept roughly equals the average difference between TDCO and ECO for that patient.

The multiple correlation coefficient, R^2 , from this analysis does not measure the linear correlation between TDCO and ECO; rather, it measures the percentage of variability in ECO explained by the variability in TDCO and patient calibration error. On the other hand, R^2 from SLR analysis is a measure of the linear correlation between TDCO and ECO. It measures the variability in ECO because of TDCO alone. The difference between the two correlation coefficients gives a sense of how much of the variability in ECO is due to varying calibration errors among patients. For the 112 epochs, the MLR $R^2 = 0.900$, whereas the SLR $R^2 = 0.181$. Calibration error clearly accounted for a great deal of the variability in ECO.

Further inspection of the data led to another observation: calibration errors for individual patients often change after cardiopulmonary bypass. Figure 3 graphically highlights this phenomenon in two pa-

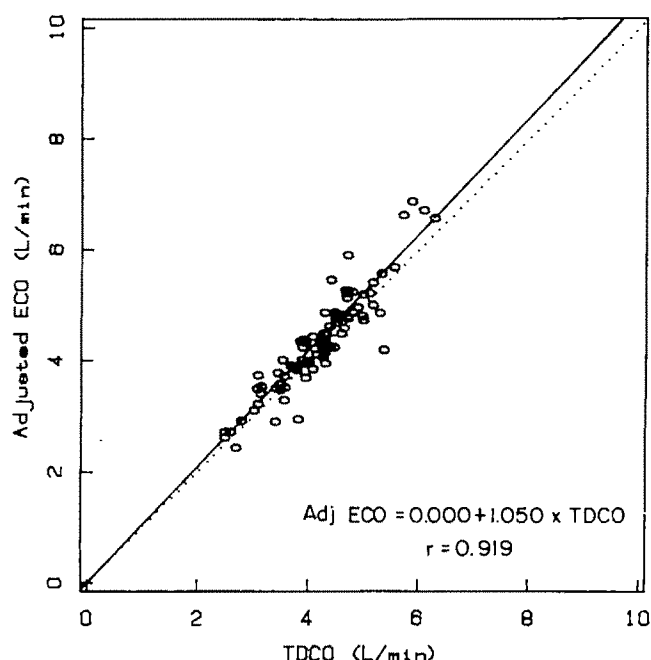


Figure 4. Adjusted esophageal Doppler cardiac output (ECO) vs thermodilution cardiac output (TDCO) for the prebypass period ($n = 82$). See Results for details.

tients. In each case, the stable relationship between TDCO and ECO before bypass was disrupted afterwards. Consequently, only the prebypass epochs were analyzed further ($n = 82$). Again, by SLR, $R^2 = 0.216$ and described the data poorly, whereas by MLR, $R^2 = 0.947$. This is to say that nearly 95% of the variability in ECO in the prebypass period was attributable to changes in TDCO and patient calibration error. The standard error of the estimate (SEE) was 0.407 L/min, and the common slope coefficient was equal to 1.050. This slope was statistically indistinguishable from one ($P > 0.1$), which suggests that ECO tracked TDCO accurately, and that the difference between ECO and TDCO was mainly due to calibration errors.

Figure 4 plots adjusted ECO vs TDCO for prebypass data. Esophageal Doppler cardiac output was adjusted by first estimating each patient's calibration error via the multiple linear regression model. A patient's calibration error is roughly equal to the average difference between ECO and TDCO for that patient. (If the estimated slope coefficient had been exactly 1.0, then the calibration error would be identical to the average difference.) Adjusted ECO values were then computed by subtracting each patient's calibration error from his/her ECO values.

The r value of 0.919 in Figure 4 is the linear correlation coefficient of adjusted ECO and TDCO. It should not be confused with the R^2 by MLR (0.947)

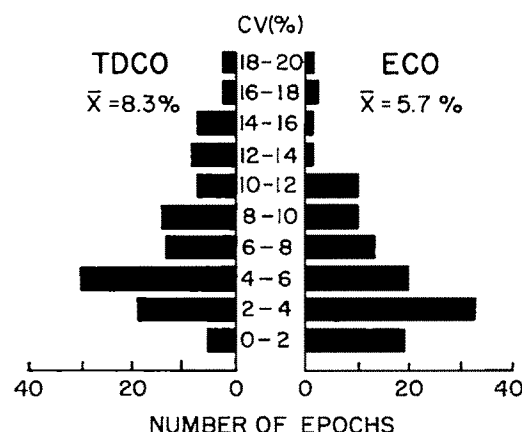


Figure 5. Within epoch variability of thermodilution cardiac output (TDCO) vs esophageal Doppler cardiac output (ECO). Bar lengths indicate the number of epochs in which the coefficient of variation (CV) fell within the specified range. \bar{X} , mean CV.

described above. However, the r value can be viewed as the correlation between ECO and TDCO if there had been no calibration error. Note that the intercept passes through the origin, suggesting that the average calibration error was zero. The calibration errors from the 16 patients could be considered random, as often causing overestimation as causing underestimation of TDCO.

Within-epoch variability of TDCO was compared to within-epoch variability of ECO by examination of the coefficients of variation (CV) for each epoch. Analyzing 112 epochs in 16 patients, the mean CV for TDCO was 8.3% (SD 5.9%), whereas the mean CV for ECO was 5.7% (SD 5.2%) (Fig. 5). The difference between these CVs was highly significant ($P < 0.001$), with TDCO being the more variable.

Aortic Measurement:

SURG-AO/UC-AO Comparison

In 23 patients, supracoronary aortic internal diameter was determined both by ultrasound (UC-AO) and by calculation from surgical measurement (SURG-AO). UC-AO ranged from 22-39 mm (mean \pm SD, 28 ± 4); SURG-AO ranged from 24-36 mm (mean \pm SD, 30 ± 3). Combining data from all 23 patients, SLR showed poor overall correlation ($r = 0.31$). In 9 (39%) of the patients, the operator had noted moderate to severe difficulty achieving a clear image of the aortic root with the A-mode transducer. In the remaining 14 patients, in whom no technical difficulties with the ultrasound measurement were noted, there was improved correlation between ultrasound and surgical measurements of aortic diameter ($r = 0.660$, SEE = 3.3 mm, $n = 14$ by SLR analysis) (Fig. 6). In this latter

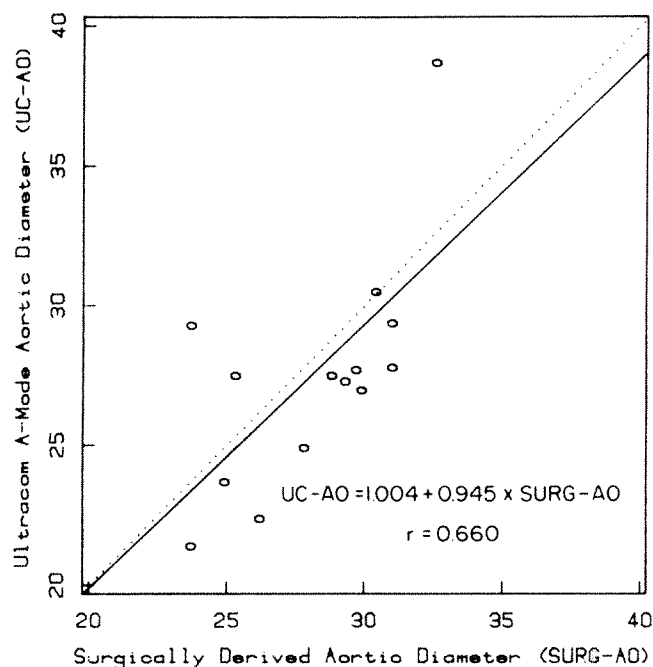


Figure 6. Scatterplot of Ultracom A-mode aortic diameter (UC-AO) and corresponding surgically derived aortic diameter (SURG-AO).

group, the ultrasound and surgical measurements were within 2 mm of each other in 6/14 patients (43%) and within 3 mm of each other in 10/14 patients (71%).

There were no complications attributable to the use of the ultrasound device. Furthermore, surgical measurements were not associated with any morbidity nor any substantial prolongation of surgical time.

Discussion

This investigation confirms our hypothesis that CO can be continuously monitored noninvasively by esophageal Doppler ultrasonography. The Ultracom[®] device has proven safe and relatively easy to use in the hands of clinical anesthesiologists. It provides a good continuous assessment of changes in CO without the need for repeated measurement procedures. As a trend monitor, its use could be simplified considerably by entering an estimated initial CO value and then simply trending CO via the esophageal probe without requiring any of the additional preliminary aortic and SSN measurements outlined above. Alternatively, aortic diameter might be estimated from a nomogram, thus obviating this step in the calibration procedure.

The high value of R^2 (0.95 by MLR) in the prebypass period strongly supports the accurate tracking capabilities of the Doppler monitoring technique. Although the overall correlation by SLR between absolute (uncorrected) Doppler CO and TDCO was poor

in this investigation, we believe this to be an underestimation of the general accuracy of the Doppler technique. A variety of factors support this conclusion, including the nature of our patient sample, limitations imposed by the surgical procedures, and limitations in applying the underlying ultrasonographic assumptions in our patients.

We were faced with substantial technical difficulties in making the complete array of ultrasound measurements in our patients. First, many had chronic pulmonary disease, which obscured the ultrasonic window through which the aorta could be visualized by A-mode echocardiography. Although none had aortic valve disease, our patients may have had distortions of aortic orientation, anatomy, or flow pattern caused by atherosclerosis, hypertension and scarring, and adhesions from previous sternotomy. The ultrasound technique assumes that the SSN Doppler beam is parallel to blood flow, that the flow velocity profile is flat across the cross-sectional area of the aorta, and that aortic dimensions remain unchanged during the surgical procedure (6). These assumptions may not have held well for our patients, who experienced moderate hemodilution and temperature swings, which affect blood viscosity, and who underwent aortic cross-clamping, which may distort aortic geometry after cross-clamp removal.

We believe that errors were introduced in the calibration steps, including both measurement of A-mode aortic diameter and SSN Doppler flow. Figure 6 reveals that considerable error still remains in the A-mode aortic measurement, even when only easily performed studies are analyzed. Although one could question the precision of our surgical measurement technique, discrepancies of this magnitude clearly imply some inaccuracy in A-mode aortic measurement in our patients. In addition, adjusting ultrasound CO by using the surgically derived aortic measurement in those patients enrolled in both studies provided excellent correlation between ECO and TDCO in one instance, but not in three others. Clearly, errors in absolute SSN measurements were also present. The surgical setting for our study is not the typical one in which the noninvasive CO monitor might be selected. In our patients, the SSN measurement had to be made promptly after intubation but before completion of the surgical preparation and incision. Measurements could not be checked and repeated to recalibrate the ultrasound machine and had to be accepted for the duration of the study. Other surgical procedures (e.g. abdominal, pelvic, urological, extremity) that give the anesthesiologist prolonged access to the SSN may allow better initial measurements and hence better absolute ultrasound/thermodilution correlation.

Intraoperative surgical maneuvers frequently caused movement of the heart in the chest, as well as more gross movements of the entire patient with forceful retraction. Cardiac, pericardial, and mediastinal movements that occurred during bypass frequently necessitated ultrasound probe adjustment upon restoration of cardiac function. Of greater concern, the distribution of flow between arch vessels and descending aorta may be altered by a period of non-pulsatile flow and rapid rewarming. In fact, the assumption that descending aortic blood flow remains a constant proportion of total left heart output as initially measured by the SSN probe must be further evaluated. Our preliminary data would indicate otherwise, because the calibration offset between TDCO and ECO was often greatly altered upon emergence from bypass (Fig. 3). Recent demonstration of a reversal of the usual relationship between aortic and radial artery pressure immediately after bypass also supports the concept of an alteration in flow distribution after bypass (12).

Finally, the choice of TDCO as the "Gold Standard" with which to compare Doppler CO raises a number of questions (13). Undoubtedly, thermodilution is the clinical standard, especially for measurement during anesthesia and surgery. However, thermodilution has many technical problems, including the consideration that respiration may have profound influences upon right heart output (14,15) and that alterations in indicator injection techniques can produce errors of nearly 80% (16-18). The Ultracom® monitor screen revealed the relative SV marching across in real time, fluctuating smoothly with positive pressure ventilation and changing abruptly after a premature ventricular beat. These observations contrasted with the frequent findings of widely disparate TDCO values, despite the fact that they were all obtained at end-expiration, with the same injection technique in a closely repeated sequence (epoch). In support of this clinical impression, we found a significantly greater variability of the within-epoch TDCO values as compared to the within-epoch ECO values ($P < 0.001$) (Fig. 5). Thus, the esophageal Doppler method is more precise, having better short-term reproducibility than TDCO, another point in its favor as a CO trend monitor.

As the noninvasive technique allows routine CO monitoring in patients in whom invasive monitoring is considered inappropriate, a new and very important question arises. What is the clinical value of knowing the CO or changes in CO in the absence of knowledge of cardiac filling pressures? At present, these two sets of values are available simultaneously through the use of the PA catheter, permitting calculation of vascular resistance and other derived

hemodynamic indices. Future investigations should address the utility of CO values or trends alone in aiding patient care.

In summary, we have shown that esophageal Doppler ultrasonography is a reliable, noninvasive technique that allows accurate trending of CO in patients undergoing cardiac surgery. Indeed, ECO has greater reproducibility than TDCO. With minimal experience, clinical anesthesiologists can employ this technique to monitor patients during general anesthesia. Future investigations should address the usefulness of "isolated" CO trends in guiding patient management. Improved accuracy (correlation with TDCO) with this technique would be anticipated in other surgical settings and awaits further evaluation.

The authors are indebted to Ms. Judy Wyman for manuscript preparation, Dr. Paul Eckenbrecht for data collection, Ms. Ellen Murray and Dr. Usha Dhingra for assistance with data collection and management, and Dr. Benjamin G. Covino for his helpful suggestions.

References

1. Foote GA, Schabel SI, Hodges M. Pulmonary complications of the flow-directed balloon-tipped catheter. *N Engl J Med* 1974;290:927-31.
2. Thomson IR, Dalton BC, Lappas DG, Lowenstein E. Right bundle-branch block and complete heart block caused by the Swan-Ganz catheter. *Anesthesiology* 1979;51:359-62.
3. Barash PG, Nardi D, Hammond G, et al. Catheter-induced pulmonary artery perforation: mechanisms, management, and modifications. *J Thorac Cardiovasc Surg* 1981;82:5-12.
4. Chandraratna PA, Nanna M, McKay C, et al. Determination of cardiac output by transcutaneous continuous-wave ultrasonic Doppler computer. *Am J Cardiol* 1984;53:234-7.
5. Lang-Jensen T, Berning J, Jacobsen E. Stroke volume measured by pulsed ultrasound Doppler and M-mode echocardiography. *Acta Anaesthesiol Scand* 1983;27:454-7.
6. Huntsman LL, Stewart DK, Barnes SR, Franklin SV, Colocousis JS, Hessel EA. Non-invasive Doppler determination of cardiac output in man: clinical validation. *Circulation* 1983;67:593-602.
7. Nishimura RA, Callahan MJ, Schaff HV, Ilstrup DM, Miller FA, Tajik AJ. Non-invasive measurement of cardiac output by continuous-wave Doppler echocardiography: initial experience and review of the literature. *Mayo Clin Proc* 1984;59:484-9.
8. Colocousis JS, Huntsman LL, Curreri PW. Estimation of stroke volume changes by ultrasonic Doppler. *Circulation* 1977;56:914-7.
9. Huntsman LL, Gams E, Johnson CC, Fairbanks E. Transcutaneous determination of aortic blood-flow velocities in man. *Am Heart J* 1975;89:605-12.
10. Belsley DA, Kuh E, Welsch RE. Regression diagnostics: identifying inferential data and sources of collinearity. New York, John Wiley and Sons, 1980:15.
11. Morrison DF. Multivariate statistical methods. New York, McGraw-Hill 1976:136-41.
12. Stern DH, Gerson JJ, Allen FB, Parker FB. Can we trust the direct radial artery pressure immediately following cardiopulmonary bypass? *Anesthesiology* 1985;62:557-61.

13. Schuster AH, Nanda NC. Doppler echocardiographic measurement of cardiac output: comparison with a non-golden standard. *Am J Cardiol* 1984;53:257-9.
14. Stevens JH, Raffin TA, Mihm FG, Rosenthal MH, Stetz CW. Thermodilution cardiac output measurement: effects of the respiratory cycle on its reproducibility. *JAMA* 1985;253:2240-2.
15. Snyder JV, Powner DJ. Effects of mechanical ventilation on the measurement of cardiac output by thermodilution. *Crit Care Med* 1982;10:677-82.
16. Maruschak GF, Pottier AM, Schauble JF, Rogers MC. Overestimation of pediatric cardiac output by thermal indicator loss. *Circulation* 1982;65:380-3.
17. Plachetka JR, Larsen DF, Solomon NW, Copeland JG. Comparison of two closed systems for thermodilution cardiac outputs. *Crit Care Med* 1981;9:487-9.
18. Wetzel RC, Latson TW. Major errors in thermodilution cardiac output measurement during rapid volume infusion. *Anesthesiology* 1985;62:684-7.

Pharmacokinetics and Pharmacodynamics of Alfentanil Infusions during General Anesthesia

Audrey Shafer, MD, Man-Ling Sung, MS, and Paul F. White, PhD, MD

SHAHER A, SUNG M-L, WHITE PF. Pharmacokinetics and pharmacodynamics of alfentanil infusions during general anesthesia. *Anesth Analg* 1986;65:1021-8.

The pharmacokinetic and pharmacodynamic properties of alfentanil were studied in 64 surgical patients. Alfentanil was administered as a loading infusion (25-130 $\mu\text{g/kg}$) followed by a maintenance infusion ($0.25-1.3 \mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$) as part of a nitrous oxide-narcotic-muscle relaxant technique. Although alfentanil doses of at least $50 \mu\text{g/kg}$ (in combination with thiopental, 2mg/kg) were required to prevent hemodynamic changes during intubation, apnea or chest wall rigidity frequently occurred with alfentanil loading infusions exceeding $75 \mu\text{g/kg}$. The alfentanil clearance rate was significantly lower in patients with liver dysfunction (2.3 ± 1.3 vs $4.2 \pm 2.0 \text{ ml}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$, mean \pm SD). In addition, the patients who required opioid antagonists to

reverse postoperative respiratory depression had lower clearance rates (1.5 ± 0.7 vs $4.1 \pm 1.9 \text{ ml}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$) and longer elimination half-life values (406 ± 304 vs $87 \pm 53 \text{ min}$). For maintenance of hemodynamic stability during superficial and intraabdominal operations, alfentanil serum concentration-response curves revealed ED_{50} values exceeding 300 ng/ml and 400 ng/ml , respectively. Our study also demonstrated a wide range of clinical responses to fixed doses of alfentanil. At equivalent doses, some patients required supplemental anesthetics, whereas others required an opioid antagonist. Careful titration of the alfentanil maintenance infusion is recommended to minimize the possibility of postoperative respiratory depression.

Key Words: ANALGESICS—alfentanil. ANESTHETICS, INTRAVENOUS—alfentanil. PHARMACOKINETICS—alfentanil

Alfentanil is a synthetic opioid with a shorter duration of effect and elimination half-life than other currently available opioid analgesics (1). Based on its pharmacokinetic profile, continuous infusion of alfentanil has been suggested as the preferred route of administration (1,2). Use of a constant infusion instead of repeated bolus injections of an opioid analgesic like alfentanil during an operation would be expected to produce greater stability with regard to its clinical effects because it would minimize the "peaks and valleys" in drug concentration (3,4). It has been suggested that the use of pharmacokinetic variables to determine opioid drug infusion rates would improve our ability to control precisely their effects (5). Available pharmacokinetic data on alfentanil are based

largely on serum samples obtained after single bolus injections in small groups of patients or volunteers (1,6-8).

In order to rapidly achieve a therapeutic alfentanil concentration at its site of action within the central nervous system, a loading dose of alfentanil based on the volume of the central compartment should precede or coincide with the administration of the maintenance infusion (9,10). We chose to administer two sequential infusions of alfentanil at differing loading and maintenance rates in an attempt to define a therapeutic steady state serum concentration range during general anesthesia when a nitrous oxide-narcotic-muscle relaxant anesthetic technique was used. We administered the loading dose of alfentanil as an infusion in order to minimize side effects (9).

The pharmacokinetics and pharmacodynamics of alfentanil were evaluated during both superficial and intraabdominal surgical procedures. By maintaining constant infusion rates in patients scheduled to undergo operations without significant changes in fluid volume, we were able to study the feasibility of achieving steady state alfentanil levels during surgery. Finally, pharmacokinetic variables associated with a delayed recovery after alfentanil infusion were assessed.

Supported in part by a research grant from Janssen Pharmaceutica. Alfentanil (Alfenta[®]) was a gift from Janssen Pharmaceutica, Piscataway, New Jersey.

Received from the Department of Anesthesia, Stanford University School of Medicine, Stanford, California. Accepted for publication May 12, 1986.

Address correspondence to Dr. White, Department of Anesthesia, S-268C, Stanford University School of Medicine, Stanford, CA 94305.

Table 1. Alfentanil Dosage Schedule, Steady State Alfentanil Levels (C_{ss}), and the Percentage of Patients in Each Dosage Group Judged to be Adequately Anesthetized during the Maintenance Period

Group Number	Surgical procedure	n	Sex (M/F)	Loading infusion ($\mu\text{g/kg}$)	Maintenance infusion rate ($\mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$)	Alfentanil C_{ss} levels ^a (ng/ml)	Adequate anesthesia ^b (%)
1	Superficial	12	2/10	25	0.25	79 \pm 37	50
2	Superficial	9	5/4	50	0.50	133 \pm 63	66
3	Superficial	7	1/6	75	0.75	190 \pm 77	72
4	Intraabdominal	10	2/8	40	0.40	104 \pm 39	20
5	Intraabdominal	16	3/13	80	0.80	271 \pm 94	75
6	Intraabdominal	10	0/10	130	1.30	327 \pm 72	80

^aValues are mean \pm SD.^bChanges in hemodynamic variables remained within 20% of baseline values without evidence of autonomic hyperactivity (e.g., diaphoresis, lacrimation).

Methods

Sixty-four unpremedicated male and female patients, ASA class I–II, scheduled for superficial ($n = 28$) or intraabdominal ($n = 36$) surgical procedures, gave written informed consent. Superficial (S) procedures involved the integument, e.g., mastoplasty, abdominoplasty, mastectomy, or hand/finger surgery. Intraabdominal (A) procedures involved a midline or low transverse abdominal incision, e.g., tuboplasty, hysterectomy, staging laparotomy, or bowel resection. Approval for the study was obtained from the Medical Committee for the Protection of Human Subjects in Research at Stanford University and the Research Advisory Panel for the State of California. Baseline data included age, sex, weight, habits (cigarette, alcohol and drug use), and screening liver function tests. Patients with a history of opioid drug abuse were excluded. Patients were sequentially assigned to a dose regimen group (Table 1).

Blood pressure and heart rate were recorded at 1–2-min intervals using a DinamapTM hemodynamic monitor. A Puritan-BennettTM capnograph was used to monitor end-tidal carbon dioxide (PET_{CO_2}) and respiratory rate. Metocurine, 2 mg, and droperidol, 0.5–1.0 mg, were administered intravenously immediately before starting a 5-min loading infusion of alfentanil (25, 50, or 75 $\mu\text{g/kg}$ in the S procedures, or 40, 80, or 130 $\mu\text{g/kg}$ in the A procedures). Alfentanil was infused into a peripheral vein using an AutosyringeTM pump. Signs of apnea and muscle rigidity during the loading infusion were noted. Patients were considered apneic when no spontaneous respirations occurred, and when they would not breathe despite repeated verbal commands. Muscle rigidity was defined as the inability to adequately ventilate apneic patients after insertion of an oral or nasal airway. After the alfentanil loading infusion and the intravenous administration of thiopental, 2 mg/kg, and succinylcholine, 1.5 mg/kg, tracheal intubation was

performed. Supplemental bolus doses of thiopental, 50 mg intravenously (IV), were injected during or immediately after laryngoscopy if patient movement or hemodynamic changes (e.g., increases in blood pressure or heart rate exceeding 20% of the baseline values) indicated inadequacy of the initial dose.

The maintenance infusion of alfentanil was started immediately after the loading infusion and corresponded to the loading dose (0.25, 0.50, or 0.75 $\mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$ for the S procedures or 0.4, 0.8, or 1.3 $\mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$ for the A procedures, respectively). Nitrous oxide, 70% in oxygen, and metocurine, 0.1–0.3 mg/kg IV (as needed for surgical relaxation), were administered as adjuvants to the alfentanil infusion. During the operation, arterial blood gas tensions were measured and ventilation adjusted to maintain normocarbica. Heated airway circuit humidifiers were used to maintain body temperature within the 35–37°C range. Patients were observed for signs of excessive sympathetic activity (e.g., lacrimation, diaphoresis), response to verbal command, or spontaneous motor activity. Patients with signs of inadequate hypnosis (e.g., opening eyes) received thiopental, 50 mg IV. If clinical signs of inadequate anesthesia persisted, a potent inhalational agent (e.g., isoflurane, 0.25–0.5%) was administered. Tachycardia or hypertension was defined as heart rate or mean arterial pressure greater than 120% of baseline values for a period of at least 10 min. Patients with tachycardia were treated with propranolol, 0.25 mg IV bolus injections. Patients with hypertension were treated with a sodium nitroprusside infusion (0.5–2.0 $\mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$). Patients who required additional thiopental, isoflurane, propranolol, or nitroprusside during the operation were judged to be inadequately anesthetized. However, hemodynamic data from patients who required supplemental agents were included in our data analysis.

At the end of surgery, the alfentanil infusion was discontinued; neostigmine, 2.5–5 mg, and glycopyrrolate, 0.4–0.8 mg, were administered intravenously;

and nitrous oxide was discontinued. Patients who failed to resume adequate spontaneous ventilation ($PET_{CO_2} < 50$ torr) within 15 min after discontinuing the nitrous oxide, or who had respiratory rates less than 8 breaths/min in the recovery room received naloxone, 0.04 mg IV bolus injections. Twenty-four hours after surgery, patients were questioned regarding intraoperative recall and postoperative side effects.

A peripheral venous catheter inserted into the arm contralateral to the infusion site was used to obtain blood samples for alfentanil assay. Samples were collected every 5 min for 20 min, then every 10 min for 40 min, and finally every 15-30 min for 6 hr. Serum alfentanil concentrations were measured by a modified radioimmunoassay method (11,12). Pharmacokinetic variables [intercompartmental microconstants k_{10} , k_{12} , and k_{21} , volume of the central compartment (V_c), and volume of distribution at steady state ($V_{d_{ss}}$)] were calculated by using differential equation two-compartment modelling with the Prophet system procedure Diffee (13). The remaining variables (distribution rate constant, α , and half-life, $t_{1/2\alpha}$; elimination rate constant, β and half-life, $t_{1/2\beta}$; and clearance, Cl) were calculated using standard formulas (14). Pharmacokinetic analysis was not modified for addition of supplemental drugs (e.g., isoflurane).

Nonlinear least-squares regression analysis was used to fit curves to serum alfentanil levels. The alfentanil serum concentration at steady state (C_{ss}) was calculated from fitted curves of individual patient data. Statistical evaluation included Duncan's multiple range testing (hemodynamic data), Students' *t*-test, linear regression analysis (for continuous data), χ^2 test, and Mann-Whitney rank sum testing (for non-normally distributed data). Values of *P* less than 0.05 were considered significantly different from the control (baseline) values. Data are presented as mean values \pm SD.

Results

There were no significant differences in age (35 ± 11 yr), weight (69 ± 17 kg), or duration of maintenance infusion (173 ± 68 min) in the S and A groups. Although group 2 had a significantly higher male:female ratio (Table 1), no significant differences were found in the data grouped by sex.

Figure 1 demonstrates the clinical responses to the loading infusion in patients grouped according to dosage regimen. Forty-three percent of patients who received the lowest alfentanil loading dose ($25 \mu\text{g/kg}$) required supplemental thiopental (after the initial 2-mg/kg induction dose), whereas only 13% of the patients receiving 75-80 $\mu\text{g/kg}$ needed additional thio-

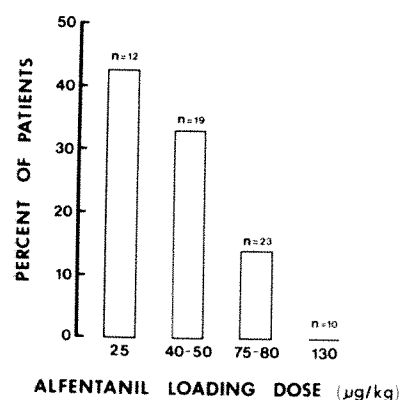


Figure 1. The percentage of patients, grouped by alfentanil loading dose, who required supplemental thiopental (after the initial 2 mg/kg dose) for tracheal intubation.

pental. None of the patients who received the highest alfentanil dose ($130 \mu\text{g/kg}$) needed supplemental thiopental. No patient receiving less than $75 \mu\text{g/kg}$ of alfentanil experienced apnea or rigidity. Seven of 23 patients (30%) who received 75-80 $\mu\text{g/kg}$ of alfentanil and six of ten patients (60%) who received $130 \mu\text{g/kg}$ became apneic during the loading infusion. Four patients exhibited signs of chest wall rigidity during the loading alfentanil infusion despite pretreatment with metocurine. One patient had received 80 $\mu\text{g/kg}$ of alfentanil, and the other three had received $130 \mu\text{g/kg}$ of alfentanil. In all cases, the rigidity occurred at the end of the infusion and resolved promptly after administration of thiopental and succinylcholine.

Figures 2 and 3 illustrate mean arterial pressure (MAP) and heart rate data for patients grouped according to their dosage regimen. Preanesthetic baseline hemodynamic data (MAP and heart rate values of 92 ± 11 mm Hg and 84 ± 15 beats/min, respectively), derived from the average of 2-4 measurements made prior to administration of any drugs, did not differ significantly in the S and A groups. A significant decrease in MAP during the loading infusion was found in patients receiving 80 or $130 \mu\text{g/kg}$ of alfentanil (77 ± 11 and 79 ± 8 mm Hg, respectively). During intubation, heart rate was significantly increased in the low-dose A group (107 ± 17 mm Hg), and MAP was significantly higher in the low-dose S group (107 ± 25 mm Hg). Conversely, MAP was significantly lower in the high-dose A group (76 ± 9 mm Hg). Relative bradycardia occurred in five of the six groups (62 ± 11 , 59 ± 8 , 71 ± 13 , 68 ± 10 , and 61 ± 6 beats/min for groups 2-6) during the surgical preparation period, although MAP decreased significantly only in the higher dosage groups (75 ± 8 , 73 ± 10 , and 75 ± 9 mm Hg for groups 3, 5, and 6). Hypertensive responses to skin incision were noted

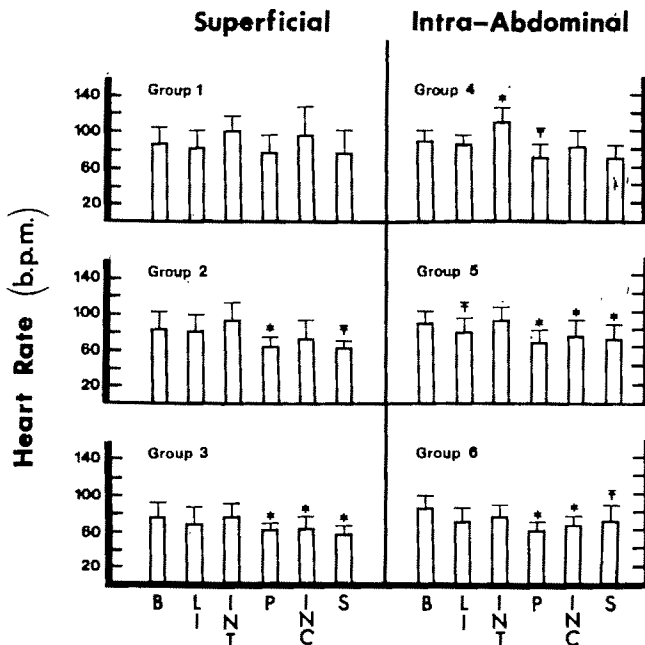


Figure 2. Heart rate (b.p.m., beats per min) changes during anesthesia in the various study groups. Mean and standard deviation for preanesthetic baseline (B); after loading infusion (L), intubation (INT), surgical preparation (P), skin incision (INC), and during surgery (S). Significant differences from preanesthetic baseline: * $P < 0.01$, † $P < 0.05$.

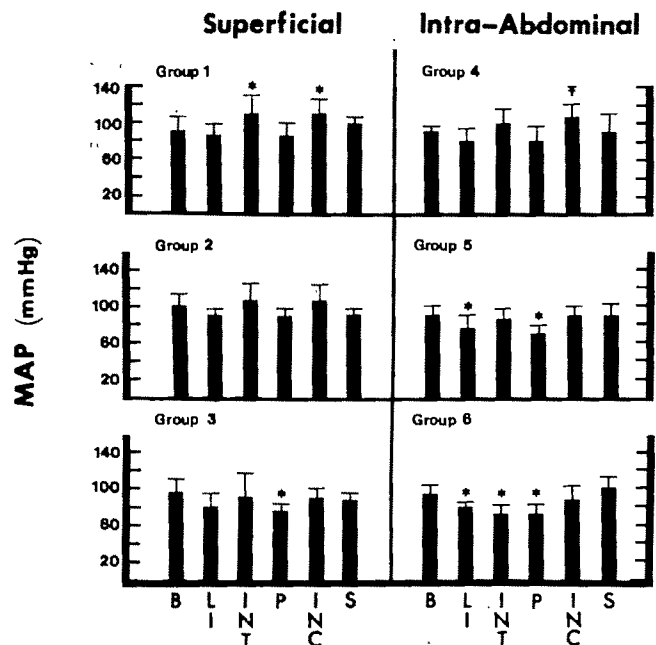


Figure 3. Mean arterial pressure (mm Hg) changes during anesthesia in the various study groups. Mean and standard deviation for preanesthetic baseline (B); after loading infusion (L), intubation (INT), surgical preparation (P), skin incision (INC), and during surgery (S). Significant differences from preanesthetic baseline: * $P < 0.01$, † $P < 0.05$.

Table 2. Relationship between Steady State Alfentanil Concentration and Clinical Response during General Anesthesia

Alfentanil C_{ss} (ng/ml)	Superficial group			Intraabdominal Group		
	<i>n</i>	Inadequate ^a (%)	Adequate ^b (%)	<i>n</i>	Inadequate ^a (%)	Adequate ^b (%)
0-100	11	55	45(0)	4	75	25(0)
101-200	14	36	64(0)	10	60	40(0)
201-300	3	33	66(0)	10	40	60(30)
>300	—	—	—	11	9	91(27)

^aPercentage of patients requiring supplemental drugs to suppress hemodynamic and/or autonomic responses to surgical stimulation.

^bPercentage of patients in each alfentanil C_{ss} group requiring opioid antagonists to reverse postoperative respiratory depression shown in parentheses.

in the lowest-dose groups for both types of operative procedures (110 ± 14 and 104 ± 14 mm Hg for groups 1 and 4). Decreased heart rate persisted in the higher dose groups despite skin incision (60 ± 13 , 73 ± 14 , and 66 ± 8 beats/min for groups 3, 5, and 6) and subsequent surgical stimulation (59 ± 6 , 55 ± 8 , 71 ± 14 , and 73 ± 16 beats/min for groups 2, 3, 5, and 6).

During surgery, six patients required sodium nitroprusside (three patients in group 1, two patients in group 2, and one patient in group 4), two needed propranolol (one patient each in groups 1 and 5), ten received thiopental (two patients each in groups 1 and 3, three patients in group 2, and one patient each in groups 4, 5, and 6), and one patient in group 5 required isoflurane. Two patients in group 4 had prom-

inent diaphoresis, which persisted for 30-60 min. However, in no case was the alfentanil infusion rate decreased or discontinued because of unacceptable hypotension or bradycardia during the maintenance period.

Mean steady state alfentanil levels ranged from 79 to 190 ng/ml and from 104 to 327 ng/ml in the S and A groups, respectively (Table 1). The percentage of patients who were judged adequately anesthetized ranged from 50 to 72% and from 20 to 80% for the S and A groups, respectively. The relationship between alfentanil concentration at steady state and clinical response during surgery is summarized in Table 2. The six patients who required naloxone for postoperative respiratory depression had steady state alfen-

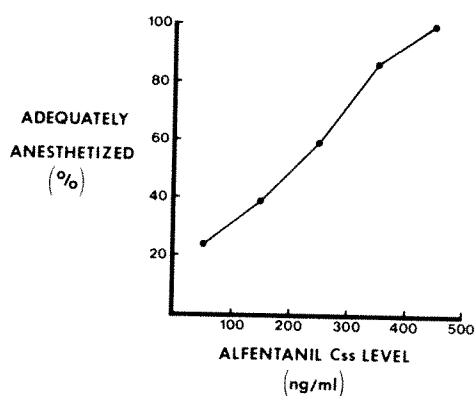


Figure 4. Percent of patients undergoing intraabdominal surgery judged adequately anesthetized (hemodynamic variables remained within 20% of baseline values) without evidence of autonomic hyperactivity. Patients are grouped according to alfentanil concentration during the maintenance infusion, at 100-ng/ml intervals.

tanil concentrations in excess of 200 ng/ml. All patients who required naloxone postoperatively were judged to be adequately anesthetized during the operation. In the A groups, the higher the serum alfentanil concentration, the greater the percentage of patients who were adequately anesthetized (Fig. 4). Interpolation of this alfentanil concentration-effect curve yields an ED₅₀ of approximately 200 ng/ml and an ED₉₅ of approximately 400 ng/ml for adequate analgesia in conjunction with nitrous oxide and muscle relaxants for intraabdominal surgery. In the A groups, only three of the study patients achieved steady state alfentanil concentration in excess of 400 ng/ml.

No patient had recall of intraoperative events. The most common postoperative side effect was nausea and vomiting (44%). This occurred despite prophylactic administration of droperidol and passage of a nasal (or oral) gastric tube after induction of anesthesia to minimize the accumulation of gas and fluid in the stomach during the operation. Nevertheless, only 17% of these patients required postoperative administration of an antiemetic medication to control their symptoms. There were no significant differences between the various dosage groups with respect to the incidence of postoperative nausea or vomiting.

Pharmacokinetic variables were independent of maintenance infusion rate (0.25–1.3 $\mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$), duration of infusion (59–385 min), weight (40–113 kg), age (18–59 yr), sex, type of surgery, or history of alcohol, cigarette, or drug use. Inadequate blood sampling and/or marked variability in serum level data during the maintenance infusion precluded formal pharmacokinetic analysis in seven patients. Preoperatively, 11 patients had mild elevations in serum liver enzyme activity (Table 3). Clearance rate, β , and k_{10} were significantly lower in these patients

Table 3. Abnormal Liver Function Tests Noted on Preoperative (Screening) Laboratory Studies

Patient number	SGPT ^a	SGOT ^b	LDH ^c	AP ^d
02	—	42	267	123
12	—	—	—	135
26	—	—	211	—
28	—	—	—	128
29	—	—	217	—
31	—	—	218	—
36	53	—	—	—
37	58	—	—	—
40	62	—	406	—
49	81	—	—	356
55	—	—	241	—

^aSGPT, serum glutamic-pyruvic transaminase (normal range: 0–45 IU/L).

^bSGOT, serum glutamic-oxaloacetic transaminase (normal range: 0–41 IU/L).

^cLDH, lactic dehydrogenase (normal range: 60–200 IU/L).

^dAP, alkaline phosphatase (normal range: 30–115 IU/L).

(Table 4). Data for one patient without baseline liver function tests are excluded. Three of the six patients who required naloxone postoperatively had laboratory evidence of preoperative hepatic dysfunction. Overall, 30% of the patients with hepatic dysfunction required naloxone compared to 6% of the patients with normal liver function tests. Patients with postoperative respiratory depression requiring treatment with an opioid antagonist had significant decreases in clearance rate, α , β , k_{10} , and k_{21} values and a significant increase in $t_{1/2\beta}$ (Table 4).

Discussion

Our study confirms pharmacokinetic data obtained in studies involving smaller numbers of patients given alfentanil as either a bolus (1,6–8) or a continuous infusion (15). Marked alterations in alfentanil pharmacokinetics in the presence of cirrhotic liver disease have been reported (16). Because alfentanil clearance is dependent on hepatic metabolism, these pharmacokinetic differences were not unexpected. Although none of our patients had clinically significant hepatic disease, liver function tests were mildly abnormal in 11 asymptomatic patients (Table 3). These patients had decreased alfentanil clearance rates that resulted in prolonged terminal elimination half-life values (Table 4).

More prominent changes in pharmacokinetics were noted in patients requiring naloxone to reverse postoperative respiratory depression (Table 4). Half of these patients appeared to have normal liver function. Other investigators have reported that an apparently normal patient with an unexpectedly low clearance rate value

Table 4. Pharmacokinetic Parameters in Patients with Normal or Abnormal Liver Function Tests (LFT), and in Patients Who Did or Did Not Require Naloxone

Variable	Normal LFT (n = 46)	Abnormal LFT (n = 10)	No naloxone (n = 51)	Naloxone (n = 6)
Clearance (ml·kg ⁻¹ ·min ⁻¹)	4.2 ± 2.0	2.3 ± 1.3 ^a	4.1 ± 1.9	1.5 ± 0.7 ^b
Vd _{ss} (L/kg)	0.47 ± 0.25	0.47 ± 0.21	0.47 ± 0.29	0.68 ± 0.29
V _c (L/kg)	0.20 ± 0.09	0.22 ± 0.09	0.21 ± 0.09	0.18 ± 0.07
α (min ⁻¹)	0.18 ± 0.09	0.16 ± 0.13	0.19 ± 0.10	0.09 ± 0.06 ^b
t _{1/2} α (min)	5 ± 3	8 ± 7	5 ± 3	12 ± 6
β (min ⁻¹)	0.010 ± 0.004	0.006 ± 0.004 ^a	0.010 ± 0.004	0.002 ± 0.001 ^b
t _{1/2} β (min)	104 ± 72	176 ± 119	87 ± 53	406 ± 304 ^b
k ₁₀ (min ⁻¹)	0.022 ± 0.010	0.011 ± 0.005 ^a	0.021 ± 0.009	0.009 ± 0.004 ^b
k ₁₂ (min ⁻¹)	0.07 ± 0.04	0.05 ± 0.04	0.07 ± 0.04	0.06 ± 0.05
k ₂₁ (min ⁻¹)	0.10 ± 0.09	0.10 ± 0.10	0.10 ± 0.09	0.02 ± 0.01 ^b

Values are mean ± SD.

Abbreviations: Vd_{ss}, volume of distribution at steady state; V_c, volume of the central compartment; α, distribution rate constant; t_{1/2} α, distribution half-life; β, elimination rate constant; t_{1/2} β, elimination half-life; k₁₀, k₁₂, k₂₁, intercompartmental microconstants.^aSignificantly different from values for patients with normal liver function tests, *P* < 0.05.^bSignificantly different from values for patients who did not require naloxone, *P* < 0.05.

for alfentanil (17) was subsequently shown to be a "debrisoquine hypometabolizer" (up to 10% of some populations have this type of genetic polymorphism) (18). More recent evidence suggests that some patients may be slow metabolizers of drugs such as alfentanil because they possess an abnormal cytochrome P-450 isozyme (19). Thus, even though alfentanil has a smaller volume of distribution and shorter elimination half-life than other currently available opiates in most healthy individuals, polymorphic oxidation of alfentanil may lead to a decreased clearance rate in some patients, resulting in a prolonged elevation of plasma levels during the postoperative period. Clearly, this normally "short-acting" opioid analgesic has the potential to cause clinically significant postoperative ventilatory depression (20-23).

We found no correlation between age and pharmacokinetic parameters in our healthy adults, all of whom were under 60 yr of age. However, these data may not apply to patients at the extremes of age (24). Another study showed decreased clearance and prolonged elimination half-life values for alfentanil in elderly patients (68-91 yr) compared with healthy young adults (27-44 yr) (25). Interestingly, both the highest (12.5 ml·kg⁻¹·min⁻¹) and lowest (1.8 ml·kg⁻¹·min⁻¹) clearance values were recorded in the elderly group. Because of alfentanil's marked pharmacokinetic variability, it was not possible to accurately predict how one should alter the dose for the individual elderly patient.

Although we found no consistent relationship between the clearance rate and the duration of the infusion, a reduction of hepatic clearance of alfentanil in patients undergoing prolonged intraabdominal surgical procedures (26) and increasing alfentanil lev-

els during a continuous infusion (15) have been reported. Decreased hepatic blood flow secondary to surgical manipulation, anesthetic agents, and/or hypovolemia, could explain these observations as well as our inability to achieve steady-state alfentanil levels in seven of the study patients. Further studies are needed to assess the effects of intraabdominal surgical manipulations on hepatic blood flow during nitrous oxide-narcotic-relaxant anesthesia.

In our unpremedicated patient population, an alfentanil loading dose of 25-50 μg/kg in combination with thiopental (2 mg/kg) and succinylcholine was often inadequate for maintenance of hemodynamic stability during laryngoscopy and intubation. More marked alterations in hemodynamic variables would have been observed if supplemental thiopental (50-100 mg) had not been administered. A larger dose of thiopental (4 mg/kg) in combination with alfentanil (30 μg/kg) has been found to block hemodynamic changes during intubation (27); conversely, a higher dose of alfentanil alone (80-125 μg/kg) in premedicated cardiac patients was associated with hemodynamic stability (28,29). However, higher doses of either induction agent can lead to unwanted side effects, e.g., hypotension with thiopental and chest wall rigidity with alfentanil. Indeed, we had a 30% incidence of chest wall rigidity in patients receiving 130 μg/kg of alfentanil.

By using fixed-rate infusions of alfentanil, we were able to evaluate our data in a dose-response fashion. Even at the highest infusion rate used for patients undergoing superficial surgery, approximately 30% of patients were judged clinically to be inadequately anesthetized. Our data predict that the alfentanil ED₉₅ for a superficial procedure exceeds 300 ng/ml. Further

studies with infusion rates greater than our highest dose, $0.75 \mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$, would be necessary to establish the upper limit of the dose-response curve for this patient population. Alternatively, alfentanil may be incapable of producing an adequate depth of anesthesia in some unpremedicated patients when used as an adjunct to nitrous oxide (Tables 1 and 2).

In our A group, a concentration-effect curve was constructed, with the alfentanil ED_{95} estimated to be 400 ng/ml. Unfortunately, when these high levels of alfentanil are required during the operation, postoperative respiratory depression may result. In a study of patients receiving etomidate and alfentanil (steady state alfentanil level of 450 ng/ml), extubation was delayed for 22 min after surgery (42 min after terminating the infusion) (30). Other investigators have reported an alfentanil ED_{95} of 400 ng/ml for patients undergoing intraabdominal surgery; however, no postoperative respiratory depression was found because the alfentanil infusion rate had been titrated to the patient's clinical response (31,32).

A second reason for titrating the alfentanil dose to effect is to overcome pharmacokinetic and pharmacodynamic variability among individual patients. Up to a five fold range of average maintenance serum alfentanil concentrations resulted during identical infusion regimens. Furthermore, patients with similar serum levels had a range of responses from inadequate anesthesia to postoperative respiratory depression (Table 2). Alfentanil's rapid onset and short duration of action should allow for improved control of effect (compared with other opioid analgesics) (33), especially when administered as a variable rate infusion (4). We would recommend adjusting the alfentanil infusion in a regulated manner analogous to the inhalational (volatile) agents.

One potential study design flaw was the sequential assignment of patients to dosage groups. Because only limited dose-response data were available on the use of alfentanil infusions at the time of the study, we felt that optimal patient safety mandated the use of lower doses at the initiation of the study. Ideally, dose-response studies would utilize random assignment to decrease bias. In addition, although we used fixed-rate infusions for achieving steady state drug levels in order to assess pharmacokinetic and pharmacodynamic variability, they are not recommended in the operating room because of the potential for drug accumulation during a prolonged surgical procedure.

In conclusion, an alfentanil infusion can be used as an adjunct to nitrous oxide and muscle relaxants for superficial and intraabdominal surgery. Careful titration to achieve the desired clinical effect is im-

portant because of interpatient variability in pharmacokinetic data and pharmacodynamic responses. Although alfentanil has been described as "a kinetically predictable narcotic analgesic," (2) some otherwise healthy individuals may manifest a decreased hepatic clearance rate for alfentanil, resulting in a delayed recovery. As with any potent opioid agonist, precautions must be taken for possible postoperative respiratory depression.

References

1. Bovill JG, Sebel PS, Blackburn CL, Heykants J. The pharmacokinetics of alfentanil (R39209): a new opioid analgesic. *Anesthesiology* 1982;57:439-43.
2. Stanski DR, Hug CC. Alfentanil—A kinetically predictable narcotic analgesic. *Anesthesiology* 1982;57:435-8.
3. de Lange S, de Buijtin N, Stanley TH, Boscoe MJ. Alfentanil-oxygen anesthesia: comparison of continuous infusion and frequent bolus techniques for coronary artery surgery. *Anesthesiology* 1981;55:A42.
4. White PF, Coe V, Shafer A, Sung M-L. Comparison of alfentanil with fentanyl for outpatient anesthesia. *Anesthesiology* 1986;64:100-6.
5. Schwilden H. A general method for calculating the dosage scheme in linear pharmacokinetics. *Eur J Clin Pharmacol* 1981;20:379-86.
6. Camu F, Gepts E, Rucquoi M, Heykants J. Pharmacokinetics of alfentanil in man. *Anesth Analg* 1982;61:657-61.
7. Schüttler J, Stoeckel H. Alfentanil (R39209) ein neues kurzwirkendes Opioid. *Anaesthesist* 1982;31:10-4.
8. Bower S, Hull CJ. Comparative pharmacokinetics of fentanyl and alfentanil. *Br J Anaesth* 1982;54:871-7.
9. Wagner JG. A safe method for rapidly achieving plasma concentration plateaus. *Clin Pharmacol Ther* 1974;16:691-700.
10. Shand DG, Desjardins RE, Bjornsson TD, Hammill SC, Pritchett ELC. The method of separate exponentials: a simple aid to devising intravenous drug-loading regimens. *Clin Pharmacol Ther* 1981;29:542-7.
11. Michiels M, Hendriks R, Heykants J. Radioimmunoassay of the new opiate analgesics alfentanil and sufentanil. Preliminary pharmacokinetic profile in man. *J Pharm Pharmacol* 1983;35:86-93.
12. Schüttler J, White PF. Optimization of the radioimmunoassay for measuring fentanyl and alfentanil in human serum. *Anesthesiology* 1984;61:315-20.
13. Perry H. *Diffeq*, Prophet public procedures. Cambridge, Massachusetts: Bolt, Beranek, and Newman, Inc. 1982;4-43-4-62.
14. Wagner JG. *Fundamentals of Clinical Pharmacokinetics*. Hamilton, IL: Drug Intelligence Publishers Inc. 1975:82-106.
15. Fraegen RJ, Booij LHDJ, Braak GJJ, Vree TB, Heykants J, Crul JF. Pharmacokinetics of the infusion of alfentanil in man. *Br J Anaesth* 1983;55:1077-81.
16. Ferrier C, Marty J, Bouffard Y, Haberer JP, Levron JC, Duvaldestin P. Alfentanil pharmacokinetics in patients with cirrhosis. *Anesthesiology* 1985;62:480-4.
17. McDonnell TE, Bartkowski RR, Bonilla FA, Henthorn TK, Williams JJ. Nonuniformity of alfentanil pharmacokinetics in healthy adults. *Anesthesiology* 1982;57:A236.
18. McDonnell TE, Bartkowski RR, Kahn C. Evidence for polymorphic oxidation of alfentanil in man. *Anesthesiology* 1984;61:A284.

19. Henthorn TK, Spina E, Birgersson C, Ericsson O, von Bahr C. In vitro competitive inhibition of desipramine hydroxylation by alfentanil and fentanyl in human liver microsomes. *Anesthesiology* 1985;63:A305.
20. O'Connor M, Escarpa A, Prys-Roberts C. Ventilatory depression during and after infusion of alfentanil in man. *Br J Anaesth* 1983;55:217S-22S.
21. Helmers JH, Van Leeuwen L, Adam AA, Giezen J, Deen L. Double-blind comparison of the postoperative respiratory depressant effects of alfentanil and fentanyl. *Acta Anaesthesiol Belg* 1982;33:13-21.
22. Sebel PS, Lalor JM, Flynn PJ, Simpson BA. Respiratory depression after alfentanil infusion. *Br Med J* 1984;289:1581-2.
23. Shafer A, Sung M-L, White PF. Differences in pharmacokinetics contribute to postoperative respiratory depression after an alfentanil infusion. *Anesthesiology* 1985;63:A283.
24. Van Peer A, Levron JC, Noorduyn H, Heykants J. Overview of the clinical pharmacokinetics of alfentanil. *Acta Anaesthesiol Belg* 1984;35:261-3.
25. Helmers JH, Van Peer A, Woestenborghs R, Noorduyn H, Heykants J. Alfentanil kinetics in the elderly. *Clin Pharmacol Ther* 1984;36:239-43.
26. Reitz J, MacKichan JJ, Hoffer L, Kryc J, Howie MB. Reduced plasma clearance of alfentanil associated with prolonged major intra-abdominal surgery. *Anesth Analg* 1984;63:265.
27. Black TE, Kay B, Healy TEJ. Alfentanil prevents the stress responses to intubation. *Anesthesiology* 1983;59:A87.
28. Sebel PS, Bovill JG, Van der Haven A. Cardiovascular effects of alfentanil anesthesia. *Br J Anaesth* 1982;54:1185-90.
29. de Lange S, de Bruijn NP. Alfentanil-oxygen anaesthesia: plasma concentrations and clinical effects during variable-rate continuous infusion for coronary artery surgery. *Br J Anaesth* 1983;55:183S-9S.
30. Schüttler J, Schwilden H, Stoekel H. Pharmacokinetics as applied to total intravenous anaesthesia. *Anaesthesia* 1983;38S:53-56.
31. Ausems ME, Hug CC. Plasma concentrations of alfentanil required to supplement nitrous oxide anaesthesia for lower abdominal surgery. *Br J Anaesth* 1983;55:191S-7S.
32. Ausems ME, Hug CC, de Lange S. Variable rate infusion of alfentanil as a supplement to nitrous oxide anesthesia for general surgery. *Anesth Analg* 1983;62:982-6.
33. Scott JC, Ponganis KV, Stanski DR. EEG quantitation of narcotic effect: the comparative pharmacodynamics of fentanyl and alfentanil. *Anesthesiology* 1985;62:234-41.

Comparison of Resuscitation of Sheep and Dogs after Bupivacaine-Induced Cardiovascular Collapse

Gregory W. Kasten, MD, and Stuart T. Martin, MD, PhD

KASTEN GW, MARTIN ST. Comparison of resuscitation of sheep and dogs after bupivacaine-induced cardiovascular collapse. *Anesth Analg* 1986;65:1029-32.

This study evaluated interspecies sensitivity and ability to resuscitate pentobarbital anesthetized sheep and dogs after cardiovascular toxic doses of bupivacaine. Every minute, 3 mg/kg of bupivacaine was injected into the right atrium over the course of 10 sec until cardiovascular collapse occurred. While the bupivacaine was given, the animals were made apneic for 90 sec and then ventilated with 100% oxygen. After the bupivacaine administration, cardiovascular collapse occurred in the form of electromechanical dissociation progressing to asystole in dogs, whereas in sheep the predominant rhythm was ventricular fibrillation leading to asystole. Resuscitation was performed using open chest heart massage, bretylium for treatment of ventricular tachycardia and fibrillation, and epinephrine with atropine for treatment

of electromechanical dissociation or asystole. The initial dose of bupivacaine used to cause cardiovascular collapse was 3.5 ± 1.2 mg/kg in sheep and 24.6 ± 8.5 mg/kg in dogs ($P < 0.01$). All sheep and dogs were resuscitated from the first cardiovascular collapse. The resuscitation time was 2.1 ± 1.0 min in dogs and 36.9 ± 15.4 min in sheep ($P < 0.01$). All dogs could be resuscitated after two additional cardiovascular collapses induced by bupivacaine, but no sheep could be resuscitated after a second cardiovascular collapse. Concentrations of bupivacaine in cardiac tissue and serum levels of bupivacaine after the last resuscitation attempt were significantly greater in the dogs than in the sheep. We conclude that sheep are more sensitive to bupivacaine than dogs, but that even sheep can be resuscitated after cardiovascular collapse produced by bupivacaine.

Key Words: ANESTHETICS, LOCAL—bupivacaine. TOXICITY—local anesthetics.

Bupivacaine cardiovascular (CV) toxicity continues to be a topic of great interest in anesthesiology. Many animal investigations have been conducted with apparently contradictory results. For example, early data indicated that administration of 4.9–5.3 mg/kg of bupivacaine intravenously to rhesus monkeys resulted in nodal arrhythmias, but that neither ventricular arrhythmias nor cardiovascular collapse occurred (1). Liu et al. reported a mean dose of 20.4 mg/kg of bupivacaine was required for CV collapse in anesthetized dogs (2). However, other investigators have reported serious ventricular arrhythmias associated with lower doses of bupivacaine given to sheep. Kotelko et al. reported that either 2.1 or 4.2 mg/kg of bupivacaine produced serious ventricular arrhythmias in awake sheep (3). Rosen et al. reported that 4.2 mg/kg of intravenous bupivacaine resulted in CV collapse in hypoxic and acidotic sheep, none of which

could be resuscitated by pharmacologic therapy and chest massage (4). However, we recently reported that anesthetized hypoxic dogs receiving a mean cumulative dose of 64.1 mg/kg of bupivacaine can be easily and consistently resuscitated (5). Although differences in methodology exist between studies, the available data suggest that substantial differences in outcome between studies may be related to differences in species sensitivity to bupivacaine. To further examine this premise, this study evaluated the species sensitivity and ability to resuscitate sheep and dogs after CV toxic doses of bupivacaine.

Methods

Six adult mongrel dogs of either sex weighing 23.1 ± 3.1 kg and six adult sheep weighing 47.5 ± 6.8 kg were anesthetized with 30 mg/kg intravenous pentobarbital and immobilized with 0.15 mg/kg pancuronium bromide. The animals were placed in a supine position and tracheally intubated with an 8-mm inside diameter cuffed tube. Ventilation was provided with a Harvard animal ventilator using room air. A percutaneous 16-gauge arterial catheter was placed in

Funded in part with a grant from Winthrop-Breon Laboratories. Received from the Department of Anesthesiology, University of Kentucky Medical Center, and Veterans Administration Medical Center, Lexington, Kentucky. Accepted for publication May 6, 1986. Address correspondence to Dr. Kasten, Department of Anesthesiology, University of Kentucky Medical Center, Lexington, Kentucky 40536-0084.

the femoral artery to provide blood samples for measurement of gas tensions, and for recording of arterial blood pressure. A 14-gauge catheter was placed into the right atrium via the right external jugular vein. Cardiac rate and rhythm were recorded by means of a lead II ECG. A median sternotomy and pericardiectomy were performed to allow open chest heart massage.

The ECG, cardiac rhythm, heart rate, and right atrial, systolic, diastolic, and mean arterial pressures were measured and recorded throughout the experiment on a Grass model 7C polygraph. Although the animals were being ventilated with an FI_{O_2} of 0.21, arterial blood pH and gas tensions were maintained as nearly as possible within the physiologic range (pH 7.35–7.45, PaCO_2 35–45 mm Hg, and PaO_2 50–90 mm Hg) by adjusting ventilatory frequency and tidal volume. Fluid administration and urine output were measured and recorded. The time interval from the beginning of resuscitation during cardiovascular collapse until the restoration of baseline blood pressure was recorded. An infusion of lactated Ringer's solution was adjusted to maintain right atrial pressure in the range of 4–10 mm Hg.

Bupivacaine was injected via the central venous catheter into the right atrium at a dose of 3 mg/kg over the course of 10 sec every minute until ventricular tachycardia, ventricular fibrillation, or severe bradycardia with electromechanical dissociation and absent blood pressure occurred. To mimic the respiratory conditions after clinical seizures that often render patients hypoxic, the animals were made apneic for 90 sec after the first dose of bupivacaine by disconnecting the ventilator from the endotracheal tube. After the 90-sec period of apnea had elapsed, arterial blood gas tensions were measured and the animals were ventilated with 100% oxygen. If CV collapse had not occurred at this point, bupivacaine was continued at 3 mg/kg over the course of 10 sec every minute until collapse occurred.

Treatment of CV collapse was as follows. Ventricular tachycardia was treated with bretylium, 30 mg/kg, given as 5 mg/kg every 30 sec intravenously; ventricular fibrillation was treated with bretylium, 30 mg/kg, epinephrine, 1.0 mg, and DC cardioversion; and bradycardia with electromechanical dissociation or asystole was treated with epinephrine, 0.75 mg, and atropine, 0.8 mg, injected intravenously through the central venous catheter followed by 0.5 mg epinephrine and 0.4 mg atropine every 45 sec until the return of stable rhythm and blood pressure. The use of bretylium, epinephrine, and atropine was based on our prior investigations, which showed these to be effective for bupivacaine-induced cardiovascular

collapse (5). Intravenous sodium bicarbonate was given after resuscitation if arterial blood samples showed evidence of metabolic acidosis, the dose being based on the base deficit derived from standard formulas. All animals received open chest heart massage after the blood pressure decreased to zero. Fluid administration after resuscitation was continued with lactated Ringer's solution to maintain right atrial pressure between 4–10 mm Hg.

To challenge the capacity to resuscitate animals given CV toxic doses of bupivacaine, the bupivacaine administration protocol was resumed after blood pressure returned to baseline for at least 5 min without the need for additional pharmacologic support. The experimental cycle of bupivacaine-induced CV collapse followed by resuscitation was repeated until three resuscitations had been achieved or the animals could not be resuscitated. Resuscitation was continued for 1 hr before efforts were ceased in unsuccessful events. After either the third successful resuscitation or the unsuccessful attempt at resuscitation, the animals were sacrificed with KCl 100 mEq intravenously. A portion of the left ventricle was removed and an arterial serum sample was obtained for measurement of bupivacaine concentrations. The bupivacaine concentrations in serum and left ventricular myocardium were determined with a gas chromatographic method using mepivacaine as the internal standard. The bupivacaine used was commercially available, preservative-free, 0.75% solution. Epinephrine and atropine solutions were from commercially available multidose vials. Sodium bicarbonate and bretylium were from single-dose commercially available ampules. Data analysis was done with analysis of variance and Student's *t*-test for unpaired data. A probability level of $P < 0.05$ was considered statistically significant.

Results

The arterial pH and blood gas tensions were similar in both groups of animals in the control period, after 90 sec of apnea, and after the first resuscitation attempt (Table 1). In the sheep, the mean bupivacaine dose was 3.5 ± 1.2 mg/kg; a dose of 3 mg/kg of bupivacaine produced CV collapse in all but one animal, and this animal sustained CV collapse after a second dose of 3 mg/kg of bupivacaine. In contrast, all dogs required a significantly higher dose, 24.6 ± 8.5 mg/kg, of bupivacaine to cause CV collapse. In sheep, the predominant rhythm was ventricular fibrillation leading to asystole, whereas in dogs the usual response was severe bradycardia with electromechanical dissociation leading to asystole.

Table 1. Arterial Blood Gas Tensions and pH

	pH	PaCO ₂	PaO ₂
Control (FiO ₂ 0.21)			
Sheep	7.42 ± 0.04	36.4 ± 5.1	65.7 ± 10.8
Dog	7.40 ± 0.04	33.1 ± 4.7	71.8 ± 8.7
After 90 sec apnea			
Sheep	7.36 ± 0.04	40.3 ± 4.9	26.7 ± 8.3
Dog	7.35 ± 0.04	37.1 ± 5.6	29.5 ± 7.5
After first resuscitation (FiO ₂ 1.0)			
Sheep	7.40 ± 0.05	37.1 ± 4.6	181 ± 111
Dog	7.43 ± 0.04	36.5 ± 6.1	313 ± 131

Values given are mean ± SD.
^a*P* > 0.05 between groups.

All sheep and dogs were resuscitated after the first CV collapse from bupivacaine (Table 2). The resuscitation time for the first bupivacaine-induced CV collapse was 2.1 ± 1.0 min in dogs and was 36.9 ± 15.4 min for sheep (*P* < 0.01). All dogs could be resuscitated from two additional CV collapses induced by bupivacaine. However, no sheep could be resuscitated after the second CV collapse. The cumulative dose of bupivacaine after which resuscitation was possible was 76.8 ± 20.4 mg/kg in dogs and 3.5 ± 1.2 mg/kg in sheep (*P* < 0.01). The amounts of epinephrine and atropine required to effect the first resuscitation were significantly greater in sheep than in dogs.

The cardiac tissue concentrations and serum levels of bupivacaine after the last resuscitation attempt (the second unsuccessful attempt for sheep and the third successful resuscitation for dogs) were greater in the dog than in the sheep. (Table 3) The myocardial tissue/blood ratios were similar in both species.

Discussion

This study demonstrates clear species differences between dog and sheep in CV response to bupivacaine administration and in ease of resuscitation. Compared to the dog, the sheep is much more sensitive to bupivacaine and requires a much longer time to resuscitate. The reasons for the greater sensitivity to bupivacaine in sheep are not clear. However, because bupivacaine levels in both the heart and blood were greater in the dog after the third (successful) resuscitation than after the second (unsuccessful) resuscitation in sheep, a pharmacodynamic rather than a pharmacokinetic mechanism appears to be involved. Perhaps the cardiac sodium channel is more easily blocked by bupivacaine in sheep or the sympathetic nervous system more readily compensates in dogs.

Table 2. Resuscitation Results

	Dog	Sheep
Dose for first cardiovascular collapse (mg/kg)	24.6 ± 8.5 ^a	3.5 ± 1.2
Cumulative dose with which resuscitation was still possible (mg/kg)	76.8 ± 20.4 ^a	3.5 ± 1.2
Need for bretylium	0/6 ^a	6/6
Epinephrine dose for first resuscitation (mg)	1.2 ± 0.4 ^a	5.9 ± 3.1
Atropine dose for first resuscitation (mg)	1.2 ± 0.4 ^a	4.0 ± 2.1
Time for first resuscitation (min)	2.1 ± 1.0 ^a	36.9 ± 15.4

Values given are mean ± SD.

^a*P* < 0.05

Table 3. Bupivacaine Serum and Myocardial Tissue Levels

	Sheep ^a	Dog ^b
Serum concentration (μg/ml)	2.6 ± 1.1 ^c	38.0 ± 17.5
Left ventricular concentration (μg/gm)	12.5 ± 8.1 ^c	185 ± 111
Heart/blood ratio	4.9 ± 1.8	5.0 ± 2.3

Values given as mean ± SD.

^aAfter second unsuccessful resuscitation.

^bAfter third successful resuscitation.

^c*P* < 0.05.

In spite of the greatly increased sensitivity to bupivacaine after the first CV collapse, the sheep could always be resuscitated at this point. The amount of bupivacaine given to the sheep (3.5 ± 1.2 mg/kg) was more than the usual clinical dose of bupivacaine given to humans. Data available from the manufacturer's package insert suggest a maximum dose of 175 mg of bupivacaine without epinephrine. In a 70-kg person this would be 2.5 mg/kg. Thus our data suggest that even in the sensitive sheep model, cardiovascular resuscitation is consistently possible when clinically relevant doses of bupivacaine are given intravenously. This comparison does not take into account the fractionalization of the bupivacaine dose that is commonly performed clinically and should result in even lower plasma concentrations of bupivacaine after accidental intravenous administration and, in theory, should result in less cardiovascular toxicity.

The results of this investigation explain apparent differences between prior investigations of bupivacaine cardiovascular toxicity. Many animal studies have reported LD₅₀ doses of bupivacaine that are greater than clinically relevant doses of bupivacaine in humans and also associated with easy resuscitation. For

example, Liu et al. reported that the LD₅₀ of bupivacaine was 20.4 mg/kg in dogs (2). They concluded that the cardiovascular system is relatively resistant to the toxic effect of local anesthetic drugs when compared to the central nervous system. Malagodi et al. reported that 5.3 mg/kg of bupivacaine in rhesus monkeys resulted in nodal arrhythmias and not in sustained CV collapse (1). Our data demonstrate that dogs given mean cumulative doses of 64.1 mg/kg of bupivacaine can be consistently resuscitated (5). Chadwick reported that cats given a mean cardiotoxic dose of 18.4 mg/kg of bupivacaine can be resuscitated (6). In experiments on cats, deJong and Davis reported that the animals could be resuscitated after a mean dose of 11.8 mg/kg of bupivacaine (7). Recent experiments revealed that in acidotic rabbits resuscitation is still possible after intravenous bupivacaine doses of 3.0–6.0 mg/kg (8). Our preliminary, unpublished data reveal that swine can be easily resuscitated after 10 mg/kg of bupivacaine. However, Rosen et al. recently reported that hypoxic, acidotic sheep could not be resuscitated after intravenous doses of 4.2 mg/kg of bupivacaine using closed chest massage and pharmacologic therapy for 15–20 min (4). The results in our present study are dramatically different from those found by this group of investigators. Several small differences in methods may help to explain these different findings. In our study, we gave sheep a dose of bupivacaine for the initial CV collapse of 3.5 ± 1.2 mg/kg, slightly less than the dose of 4.2 mg/kg administered by Rosen et al. The sheep in our study sustained a greater degree of hypoxia (PaO₂ of 26 mm Hg) than the sheep in the study by Rosen et al. (PaO₂ of 50 mm Hg), but the degree of acidosis was greater in the animals studied by Rosen et al. (pH 7.15 vs 7.36). Rosen et al. reported that during closed chest massage, a mean arterial pressure of 50 mm Hg was difficult to obtain (4). With our open chest cardiac massage, mean pressures of 100 mm Hg were easily obtained. We believe our success was due to open chest massage, greater doses of epinephrine, and a longer duration of resuscitation. The lack of a severe acidosis in our sheep may have contributed to a successful outcome.

The animal model that most closely approximates humans with regard to bupivacaine CV toxicity is not apparent at this time. As described above, resuscitation studies in dogs, cats, rabbits, and swine show that resuscitation can be performed easily (5–8). The data in this paper suggest that sheep, although sensitive to bupivacaine, can be consistently resuscitated but require a longer duration of resuscitation. Many investigators consider primates to be an animal model similar to humans and perhaps future studies should

concentrate on this group of animals. However, Malagodi et al. reported that rhesus monkeys given convulsive doses of 5.3 mg/kg of bupivacaine at a rate of $2.0 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$, sustained nodal rhythms only and CV collapse did not occur (1). Thus it appears that clinically relevant doses of bupivacaine in the range of 1–2.5 mg/kg appear to be safe in most animal models. In fact, doses of bupivacaine of 1 mg/kg have been shown to be antiarrhythmic in several studies (9–11). Sheep appear to be the most sensitive of all animals tested with regards to bupivacaine cardiovascular toxicity and difficulty of resuscitation. In spite of this sensitivity, sheep can be resuscitated from CV toxic doses of bupivacaine. Thus, regardless of which animal model is studied, resuscitation is apparently consistently possible after clinically relevant doses of bupivacaine that are associated with CV collapse.

In summary, sheep are more sensitive to bupivacaine and require a longer period of time to resuscitate than dogs, and this sensitivity is of a pharmacodynamic nature. In spite of the increased sensitivity in sheep, resuscitation is still consistently possible. Future investigations into the mechanism of sheep sensitivity to bupivacaine may provide greater understanding of bupivacaine CV toxicity.

References

1. Malagodi MH, Munson ES, Embro WJ. Relation of etidocaine and bupivacaine toxicity to rate of infusion in rhesus monkeys. *Br J Anaesth* 1977;49:121–5.
2. Liu P, Feldman HS, Covino BM, Giasi R, Covino BG. Acute cardiovascular toxicity of intravenous amide local anesthetics in anesthetized ventilated dogs. *Anesth Analg* 1982;61:317–22.
3. Kotelko DM, Shnider SM, Dailey PA, et al. Bupivacaine induced cardiac arrhythmias in sheep. *Anesthesiology* 1984; 60:10–8.
4. Rosen MA, Thigpen JW, Shnider SM, et al. Bupivacaine induced cardiotoxicity in hypoxic and acidotic sheep. *Anesth Analg* 1985;64:1089–96.
5. Kasten GW, Martin ST. Successful cardiovascular resuscitation after massive intravenous bupivacaine overdosage in anesthetized dogs. *Anesth Analg* 1985;64:491–7.
6. Chadwick HS. Toxicity and resuscitation in lidocaine or bupivacaine infused cats. *Anesthesiology* 1985;63:385–90.
7. deJong RH, Davis NL. Treating bupivacaine arrhythmias: preliminary report. *Reg Anaesth* 1981;6:99–103.
8. Cheek DBC, Pytko S, Shnider SM, et al. Successful resuscitation after massive intravenous bupivacaine overdosage in the acidotic rabbit. *Anesthesiology* 1985;63:A246.
9. Boettner RB, Dunbar RW, Haley JV, Morrow DH. A comparison of the antiarrhythmic effects of bupivacaine and lidocaine. *South Med J* 1972;65:1328–30.
10. Dunbar R, Boettner RB, Gatz R, Pennington R, Morrow D. The effect of mepivacaine, bupivacaine, and lidocaine on digitalis induced ventricular arrhythmias. *Anesth Analg* 1970;49:761–6.
11. Chapin JC, Cushins LG, Munson ES, Schick LN. Lidocaine, bupivacaine, etidocaine, and epinephrine induced arrhythmias during halothane anesthesia in dogs. *Anesthesiology* 1980; 52:23–6.

Epidural Morphine Improves Pain Relief and Maintains Sensory Analgesia during Continuous Epidural Bupivacaine after Abdominal Surgery

N.-C. Hjortsø, MD, C. Lund, MD, T. Mogensen, MD, D. Bigler, MD, and H. Kehlet, MD, PhD

HJORTSØ N-C, LUND C, MOGENSEN T, BIGLER D, KEHLET H. Epidural morphine improves pain relief and maintains sensory analgesia during continuous epidural bupivacaine after abdominal surgery. *Anesth Analg* 1986;65:1033-6.

Twenty patients scheduled for elective major abdominal surgery were matched into two groups with regard to age, sex, height, body weight, and surgical procedure. Both groups received general anesthesia plus lumbar epidural analgesia with similar loading doses of bupivacaine 0.5% (23.1 ± 1.0 and 23.3 ± 0.8 ml) (mean \pm SEM) followed by continuous infusion of plain bupivacaine 0.5% (8 ml/hr) plus, in one group, epidural morphine (0.5 mg/hr). Pain score on a 5-point scale and sensory analgesia (pin prick) were assessed hourly for 16 hours after skin incision. If sensory analgesia decreased more than 5 segments from preoperative levels or if pain scores reached 2 (moderate pain), the patients were removed from the study, and pain was treated with other methods.

Preoperative mean (\pm SEM) sensory levels of analgesia were similar in the bupivacaine and the bupivacaine-morphine groups ($T_{3.4} \pm 0.5$ and $T_{3.3} \pm 0.4$, respectively). In the group receiving only bupivacaine, sensory analgesia regressed over time with a simultaneous increase in pain score. Thus, within 10 hr after skin incision, seven patients in this group were discharged from the study, and 16 hr after incision only one patient maintained initial level of sensory analgesia. In contrast, each patient receiving bupivacaine plus morphine had stable sensory analgesia and was completely free of pain as indicated by a mean pain score of zero during the 16-hr observation period. Thus epidural morphine may improve pain relief and maintain analgesia during continuous epidural bupivacaine administration after abdominal surgery.

Key Words: PAIN—postoperative. ANESTHETIC TECHNIQUES—epidural morphine and bupivacaine.

Epidural administration of local anesthetics and opiates has proven to be effective in the treatment of intra and postoperative pain (1,2). Although epidural analgesia has been used extensively, no regimen has led to total elimination of pain after abdominal surgery. Epidural blockade with local anesthetics in combination with light general anesthesia totally relieves pain during major abdominal surgery, but maintenance of the level of epidural analgesia and pain relief during the postoperative period is difficult due to tachyphylaxis (3,4) or other factors (5,6).

Because systemic administration of morphine may improve postoperative analgesia and maintain sensory blockade during epidural bupivacaine (7), and

because little information is available on the effect of combined epidural morphine and local anesthetics, the present study was performed to investigate the effect of continuous epidural infusion of bupivacaine plus morphine on postoperative pain and the level of sensory analgesia after major abdominal surgery procedures.

Methods

Informed consent was obtained from all patients. Twenty patients scheduled for elective major abdominal surgery were premedicated with diazepam (0.2 mg/kg) and given general anesthesia induced with thiopental (3-5 mg/kg); after precurarization with pancuronium (0.01 mg/kg), succinylcholine (1.5 mg/kg) was used to facilitate orotracheal intubation. General anesthesia was maintained with N_2O/O_2 (2:1) and halothane (0.25-0.75%). Before induction of general anesthesia an epidural catheter was inserted between

Received from the Departments of Anesthesiology and Surgical Gastroenterology, Hvidovre Hospital, Copenhagen, Denmark. Accepted for publication May 15, 1986.

Address correspondence to Dr. Hjortsø, Department of Anesthesiology, Hvidovre Hospital, 2650-Hvidovre, Denmark.

Table 1. Clinical Data (mean \pm SEM) in Patients Receiving Epidural Bupivacaine or Bupivacaine Plus Morphine for Relief of Postoperative Pain

	Age (yr)	Sex (male/female)	Height (cm)	Body weight (kg)	Type of abdominal surgery (upper/lower)
Bupivacaine	64 \pm 3	3/7	166 \pm 4	59 \pm 3	7/3
Bupivacaine + morphine	65 \pm 3	4/6	165 \pm 2	65 \pm 4	7/3
	ns	ns	ns	ns	ns

ns, not significant.

Table 2. Surgical Procedures in Patients Receiving Epidural Bupivacaine or Bupivacaine Plus Morphine for Relief of Postoperative Pain

	Upper abdominal procedure	Lower abdominal procedure
Bupivacaine (n = 10)	Gastrectomy (3) Biliary procedures (2) Closure duodenal fistula (1) Right hemicolectomy (1)	Rectosigmoid resection (2) Jejunum resection (1)
Bupivacaine + morphine (n = 10)	Biliary procedures (3) Right hemicolectomy (2) Whipple resection (1) Splenectomy (1)	Rectosigmoid resection (2) Rectal amputation (1)

L-2 and L-3 and plain bupivacaine (0.5%) was used to produce a blockade from S-5 to T-4 and above. The patients were assigned to two groups so that those given epidural bupivacaine plus morphine were similar to those given epidural bupivacaine alone with regard to age, sex, height, body weight, and whether surgery was in the upper or lower abdomen (Table 1). The surgical procedures in the two groups are listed in Table 2. To obtain prolonged continuous epidural analgesia, both groups received 0.5% plain bupivacaine (8 ml/hr). Patients in one of the two groups were also given epidural morphine (0.5 mg/hr) preceded by an epidural bolus injection of morphine (4 mg in 10 ml saline) before skin incision. The epidural infusion was started immediately after induction of general anesthesia and scheduled to continue for 16 hr after skin incision.

Pain scores on a 5-point scale (no pain, slight pain, moderate pain, severe pain and unbearable pain, respectively) and levels of sensory analgesia (pin prick, bilateral) were assessed hourly after the patients recovered from the general anesthesia. If the rostral level of sensory analgesia decreased more than 5 segments from preoperative level or pain score reached 2 (moderate pain), the patients were discharged from the study, and pain was treated using other methods.

Results

Preoperative levels of sensory analgesia were similar in the bupivacaine group and the bupivacaine—mor-

phine group ($T_{3.4} \pm 0.5$ and $T_{3.3} \pm 0.4$, respectively) (mean \pm SEM, $P < 0.05$). As seen in Figures 1 and 2, patients in the bupivacaine group dropped out of the study over time because of a decrease in sensory analgesia of more than five segments below preoperative levels and/or a simultaneous increase in pain score up to 2 (moderate pain) or above. Thus, at 10 hr after skin incision, seven patients in the bupivacaine group had been discharged from the study, and at the end of the study period (16 hr after skin incision) only one patient remained in the study, a patient with a stable sensory block and a pain score below 2. In contrast, each of the 10 patients in the bupivacaine—morphine group had stable levels of sensory analgesia with only minor fluctuations of 1–2 segments compared to preoperative levels. Furthermore, all patients in this group were completely free of pain, as indicated by a mean pain score of 0 ± 0.0 at all readings during the study period. No cardiovascular or respiratory complications were observed during the study.

Discussion

Epidural analgesia with local anesthetics is effective in preventing intraoperative pain and may be a powerful tool in pain alleviation during the postoperative period. However, several problems are associated with maintenance of analgesia by a continuous epidural blockade with local anesthetics. Tachyphylaxis, for example, has been reported during repeated epidural injection (3), as well as during continuous epidural

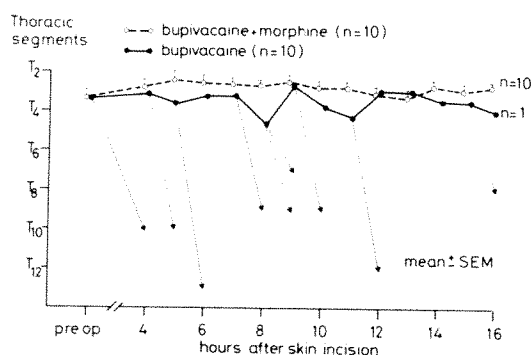


Figure 1. Changes in sensory levels of analgesia during continuous epidural infusion of bupivacaine (0.5%, 8 ml/hr) with or without epidural morphine (0.5 mg/hr) after abdominal surgery.

infusion (4). Furthermore, an unpredictable instability of sensory blockade, which could not be explained by tachyphylaxis, has been reported during prolonged postoperative epidural administration of local anesthetics (5,6).

Recently, we described a synergistic effect of systemic morphine on the extent of sensory blockade during continuous postoperative epidural infusion of bupivacaine (7). The results of the present study indicate that the addition of morphine (0.5 mg/hr) to bupivacaine administered continuously epidurally has a stabilizing effect on sensory blockade in the postoperative period, and that postoperative pain was minimal. In the 10 patients who received bupivacaine alone, the sensory blockade decreased at least 5 segments within 16 hr after skin incision, except in one patient in whom analgesia was stable. Simultaneously with the decrease in blockade, pain score increased. It should be emphasized that these patients did not receive opioids either as premedication or during the general anesthesia.

The explanation of the enhancing effect of epidural morphine may be found in the recent information on the anatomy and physiology of nociceptive systems. The prevention of sensory pain by epidural local anesthetics is effected by neuronal blockade of afferents just before their entrance into the spinal medulla. However, the regression of sensory block during continuous bupivacaine may be explained by an increase in afferent input, because experimental studies have demonstrated an increase in peripheral afferent input and in spinal cord excitability after peripheral trauma (8). Thus an increase in afferent neural transmission during the later postoperative period may override the blocking effect of epidural bupivacaine, thereby reducing sensory analgesia in the rostral part of epidural space where the epidural concentration of bupivacaine presumably is lowest. Epidural morphine

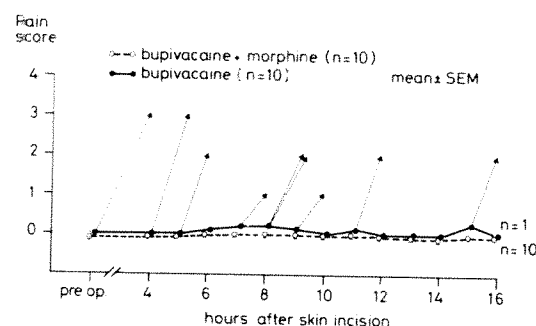


Figure 2. Changes in pain scores (0-4) during continuous epidural infusion of bupivacaine (0.5%, 8 ml/hr) with or without epidural morphine (0.5 mg/hr) after abdominal surgery.

may counteract these events both by a rostral CNS effect and by a direct effect on the spinal cord. Like systemic morphine, epidural morphine may turn on so called off-cells in the rostral ventral medulla that activate descending inhibitory pain modulating circuits, as shown in experimental models (9,10). Furthermore, the presence of morphine in the spinal cord and dorsal horn, may minimize the increase in spinal excitability after peripheral trauma.

We have not been able to find other studies on the effect of combined epidural administration of a local anesthetic and an opioid on postoperative pain and sensory analgesia. In one study (11) addition of small doses of morphine (0.2-0.4 mg) to bupivacaine during spinal anesthesia did not influence maximal spread of analgesia, and in another study increasing doses of epidural fentanyl added to epidural bupivacaine increased duration of analgesia (12), but neither of these studies addressed the issue examined in the present study.

In conclusion, the addition of morphine (0.5 mg/hr) to plain bupivacaine 0.5% (8 ml/hr) produces a stable level of sensory analgesia and a highly effective relief of pain during the initial 16 hr after major abdominal surgical procedures. These findings indicate the need for future studies to establish whether tachyphylaxis may be prevented and pain alleviation maintained during a more prolonged (2-4 days) administration of epidural bupivacaine plus morphine.

References

1. Rawal N, Sjöstrand U, Dahlström B. Postoperative pain relief by epidural morphine. *Anesth Analg* 1981;60:726-31.
2. Bromage PR, Camporesi E, Chestnut D. Epidural narcotics for postoperative analgesia. *Anesth Analg* 1980;59:473-80.
3. Bromage PR, Pettigrew RT, Corwell DE. Tachyphylaxis in epidural analgesia. I. Augmentation and decay of local anesthesia. *J Clin Pharmacol* 1969;9:30-8.

4. Renck H, Edström H, Kinnberger B, Brandt G. Thoracic epidural analgesia. II. Prolongation in the early postoperative period by continuous injection of 1.0% bupivacaine. *Acta Anaesthesiol Scand* 1976;20:47-56.
5. Bigler D, Hjortsø N-C, Kehlet H. Variation in spread of sensory and cold analgesia during intermittent postoperative epidural bupivacaine administration. *Acta Anaesthesiol Scand*, in press.
6. Scott DB, Schweitzer S, Thorn J. Epidural block in postoperative pain relief. *Reg Anesth* 1982;7:135-39.
7. Lund C, Mogensen T, Hjortsø N-C, Kehlet H. Systemic morphine enhances spread of sensory analgesia during postoperative epidural bupivacaine infusion. *Lancet* 1985;ii:1156-7.
8. Woolf CJ. Evidence for a central component of postinjury pain hypersensitivity. *Nature* 1983;306:686-8.
9. Fields HL, Vanegas H, Hentall ID, Zoeman G. Evidence that disinhibition of brain stem neurons contributes to morphine analgesia. *Nature* 1983;306:684-6.
10. Fields HL, Heinricher MM. Anatomy and physiology of a nociceptive modulatory system. *Phil Trans R Soc Lond* 1985;308:361-74.
11. Kalso E. Effects of intrathecal morphine, injected with bupivacaine, on pain after orthopaedic surgery. *Br J Anaesth* 1983;55:415-22.
12. Rucci FS, Cardamone M, Migliori P. Fentanyl and bupivacaine mixtures for extradural blockade. *Br J Anaesth* 1985;57:275-84.

Lack of Effect of Intravenous Lidocaine on Hemodynamic Responses to Rapid Sequence Induction of General Anesthesia: A Double-blind Controlled Clinical Trial

Bent Chraemmer-Jørgensen, MD, Poul Flemming Høilund-Carlsen, MD, Jens Marving, MD, and Vinni Christensen, MD

CHRAEMMER-JØRGENSEN B, HØILUND-CARLSEN PF, MARVING J, CHRISTENSEN V. Lack of effect of intravenous lidocaine on hemodynamic responses to rapid sequence induction of general anesthesia: a double-blind controlled clinical trial. *Anesth Analg* 1986;65:1037-41.

A double-blind, randomized trial was conducted in 16 women aged 20-48 yr, to assess the effect of intravenous lidocaine on the circulatory responses to rapid sequence induction of general anesthesia. None of the patients suffered from heart or lung diseases, all were scheduled for hysterectomy, and all were premedicated with 0.3 mg/kg diazepam orally 2 hr beforehand. Induction, preceded by preoxygenation, included simultaneous injection of thiopental and succinylcholine, without starting manual ventilation until the airway was secured with the endotracheal tube. Two minutes before laryngoscopy and intubation half of the patients received lidocaine, 1.5 mg/kg, intravenously (IV). The other half received an equal volume of saline. Cuff blood pressure

was measured repeatedly by an automatic recording device, and heart rate and left ventricular ejection fraction (LVEF) were monitored by a portable nonimaging nuclear probe. After laryngoscopy and intubation, mean blood pressure increased 46%, heart rate 57%, and the rate pressure product (RPP) 84% from control values in patients given lidocaine, compared to 45, 66, and 113%, respectively, in the saline group ($P > 0.05$). Pronounced, but similar decreases in LVEF were observed in the two groups, to 0.40 from 0.65 in the lidocaine group and to 0.41 from 0.65 in the saline group. In all patients, RPP reached a level considered potentially dangerous to patients with ischemic heart disease. We conclude that lidocaine, 1.5 mg/kg IV, 2 min prior to laryngoscopy and intubation does not prevent hemodynamic reactions evoked by rapid sequence induction.

Key Words: INDUCTION, ANESTHETIC—cardiovascular responses. ANESTHETICS, LOCAL—lidocaine.

Common hemodynamic reactions to induction of general anesthesia and tracheal intubation include tachycardia, arterial hypertension, and depression of left ventricular ejection fraction (LVEF) (1-6). These changes are considered potentially dangerous in patients with cardiovascular or cerebrovascular diseases because they may be associated with postoperative myocardial infarction or cerebral hemorrhage (7-10).

Among the various attempts made to depress these undesirable side effects of anesthetic induction and tracheal intubation, the administration of lidocaine, either topically or intravenously, has gained a certain

popularity, although the results have been somewhat contradictory (11-17).

In a previous study comparing the hemodynamic effects of rapid sequence induction of anesthesia and elective induction (18), tachycardia and hypertension evoked by laryngoscopy and intubation were more pronounced during rapid sequence induction, resulting, even in normal subjects, in values of rate pressure product (RPP) that in patients with coronary artery disease is often associated with myocardial ischemia during induction of anesthesia and intubation (8,19). Therefore, in the present double-blind, randomized clinical trial, we compared the effect of intravenous lidocaine with that of placebo on the circulatory responses to a rapid sequence induction of anesthesia and tracheal intubation.

Materials and Methods

Sixteen women (median age 36 yr, range 20-48 yr) scheduled for elective hysterectomy were investi-

Presented in part at the 8th World Congress of Anaesthesiologists, Manila, Philippines, January 24, 1984.

Received from the Departments of Anesthesia, Clinical Physiology and Nuclear Medicine, Gynecology, and Obstetrics, Glostrup Hospital, Glostrup, Copenhagen, Denmark. Accepted for publication May 15, 1986.

Address correspondence to Dr. Chraemmer-Jørgensen, Department of Anesthesia, Glostrup Hospital, DK-2600 Glostrup, Copenhagen, Denmark.

gated. None had a history of heart or lung diseases, and all had normal findings on physical examination, ECG and x-ray of the chest. Aside from premedication, none of the patients received any preoperative medication.

The study protocol was approved by the Copenhagen County Scientific-Ethical Committee, and informed consent from each patient was obtained. All investigations were performed in the anesthesia preparation room with the patients in the supine position.

Anesthetic Techniques

All patients were premedicated with diazepam, 0.3 mg/kg orally, 2 hr before surgery. After an initial period of 15–30 min at rest to achieve steady state conditions, the patients started breathing 100% oxygen (Fig. 1). After 1 min, pancuronium, 0.015 mg/kg, was administered for precurarization. Two minutes later, half of the patients received lidocaine, 1.5 mg/kg IV over 15 sec, whereas the other half received an equal volume of saline, 0.9%. The drugs were given in randomized order and in a double-blind fashion. One minute later, sleep was induced with thiopental, 5 mg/kg, immediately followed by succinylcholine, 1.5 mg/kg, to facilitate tracheal intubation performed with a MacIntosh blade laryngoscope and a 7.5-mm R sch tube. Both drugs were given as fast as possible. Laryngoscopy and intubation took place exactly 2 min after beginning the injection of lidocaine or saline. Manual ventilation was not started until the tracheal tube cuff was inflated, and was performed with nitrous oxide–oxygen, 6:3 L, and halothane, 1% inspired concentration aiming at normoventilation. The tube was passed by the same anesthetist in all patients and was in place within 20 sec of laryngoscopy.

Measurements

Blood pressure, heart rate, and LVEF were measured at least once every minute. All control values were obtained as the mean of 4 or 5 single determinations at the end of the initial period of rest. Thirty seconds after intubation, an arterial blood sample was drawn from all patients for blood gas analysis. Blood pressure was measured indirectly by an automatic recording device (Arterio-Sonde[®], Roche). Heart rate and LVEF were recorded by the Nuclear StethoscopeTM (Bios Inc., Valhalla, NY) i.e., a computerized, mobile, nonimaging nuclear probe allowing bedside beat-to-beat monitoring of LVEF by means of radionuclide technique. This instrument and its use during induction of anesthesia has been described in detail elsewhere (5). Radionuclide measurements were per-

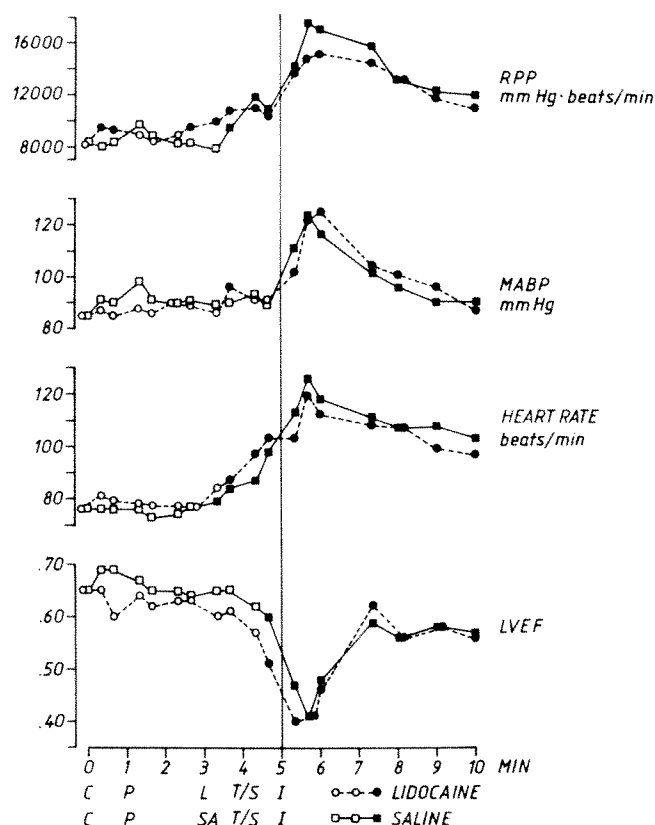


Figure 1. Relationship between rate pressure product (RPP), mean arterial blood pressure (MABP), heart rate, and left ventricular ejection fraction (LVEF) recorded in patients given lidocaine (○—○—○) or saline (□—□—□). Closed symbols indicate statistically significant changes from control values (C).

Abbreviations: P, pancuronium; L, lidocaine; SA, saline; T, thiopental; S, succinylcholine; I, laryngoscopy and intubation. For further explanations see text.

formed using red blood cells labeled with stannous pyrophosphate and 15–20 mCi ^{99m}technetium per-technetate applying a modified in vivo technique (20). The probe was placed over the chest in a 30° left anterior oblique position with 10° caudal tilt, and LVEF was calculated as the mean of a series of successive heart beats recorded within single intervals of 10 sec. With this procedure we have previously found a satisfactory agreement ($r = 0.90$) between values for LVEF obtained by the nuclear stethoscope and by γ -camera (21). After intubation, end-tidal CO₂ was monitored with a Gould Godart Capnograph MK II, keeping the CO₂ in all patients between 4.5 and 5.5%.

A nonparametric test for paired data (considering also ties) (22) was used within each of the two groups to compare each value with the initial control value. The Mann-Whitney *U*-test was used for comparisons between groups. The level of significance chosen was $2\alpha < 0.05$. All data given are median values with ranges in parentheses.

Results

There were no differences in age, weight, or control values for mean arterial blood pressure, heart rate, RPP, or LVEF in the two groups (Fig. 1). Laryngoscopy and tracheal intubation were followed by a marked increase in mean arterial blood pressure, 45% in the saline group and 46% in the lidocaine group ($P > 0.05$). Mean arterial blood pressure returned almost to control levels towards the end of the study period in both groups. There was a modest increase in heart rate after the injection of lidocaine or saline. This increase was accentuated after thiopental and succinylcholine, and was succeeded by a steep increase immediately after laryngoscopy and intubation. The maximal increase in heart rate was 66% in the control group and 57% in the lidocaine group (a statistically insignificant difference), and heart rate remained markedly elevated in both groups throughout the study. The RPP increased after laryngoscopy and intubation by 113% in the saline group and by 84% in the lidocaine group ($P > 0.05$). The maximum values for RPP, observed in both groups about 40 sec after intubation, were 17,526 in the saline group and 15,005 in the lidocaine group ($P > 0.05$). Median LVEF decreased significantly in both groups after thiopental and succinylcholine, with an even further, but equal, decrease after laryngoscopy and intubation, from 0.65 to 0.41 (37%) in the saline group and from 0.65 to 0.40 (38%) in the lidocaine group ($P > 0.05$). LVEF had not fully returned to baseline levels by the end of the study. Thirty seconds after intubation, pH averaged 7.39 (7.33-7.41), PaO_2 252 mm Hg (197-332), and PaCO_2 38 mm Hg (35-42) in the saline group and pH 7.38 (7.33-7.40), PaO_2 237 mm Hg (198-338), and PaCO_2 38 mm Hg (35-41) in the lidocaine group ($P > 0.05$).

Discussion

The mechanisms behind circulatory responses to anesthetic induction and tracheal intubation are not understood well. However, we do know they represent complex hemodynamic changes as the result of a series of successive pharmacologic and mechanical interventions. The process of laryngoscopy and intubation plays a prominent role by eliciting a possibly reflex-mediated increase in sympathetic activity (23-27) with consequent increases in heart rate and blood pressure (1-6), but in the presence of a depressed LVEF (5,6,18).

The possible suppressing effect of lidocaine on these unwanted circulatory actions have been evaluated in a number of studies (11-17). However, results are conflicting and often difficult to interpret, primarily

because of limitations and shortcomings in the design of many of these investigations.

Denlinger et al. (11) investigated the effect of intratracheal spraying with lidocaine, 4% (120 mg/70 kg), in a double-blind study of two nonhomogenous groups of patients scheduled for cardiac surgery. They observed that the increase in heart rate and blood pressure after laryngoscopy and intubation was significantly less in the treated than in the untreated group. However, in the treated group there were no differences in the increases in blood pressure observed after the two laryngoscopies performed (before and after spraying with lidocaine).

In a double-blind study, Abou-Madi et al. (12) observed a statistically only borderline protective effect of lidocaine 1.5 mg/kg given intravenously 2-3 min before laryngoscopy and intubation, in comparing two groups of patients not completely matched with regard to complicating diseases and the level of preoperative blood pressure and heart rate.

Stoelting conducted two open studies, one in patients without known heart disease (13) and another in patients scheduled for coronary artery bypass grafting (14). In both, two groups of patients receiving lidocaine either oropharyngeally (topically) or intravenously were compared with a third group, not receiving placebo, but lidocaine laryngotracheally. Consequently, these studies represent comparisons of three different methods for administering lidocaine rather than studies of the effect of lidocaine on responses to laryngoscopy and intubation. In the patients without heart disease, there was attenuation of the blood pressure response in both the group treated with topical oropharyngeal lidocaine and the group receiving lidocaine intravenously. However, this result was not reproduced in the patients with coronary artery disease. It may be added that the results of both studies might have been somewhat blurred by the fact that some of the groups received lidocaine twice, i.e., topical oropharyngeal spray plus laryngotracheal spray or intravenous administration plus topical laryngotracheal spray.

Hamill et al. (15) reported from an open study that intravenous lidocaine, 1.5 mg/kg, 1 min prior to laryngoscopy and intubation more effectively prevented intracranial hypertension and increases in heart rate and mean arterial blood pressure than did laryngotracheal lidocaine, 160 mg. However, the groups were not entirely comparable, because laryngoscopy was performed twice in the group given topical lidocaine but only once in the group receiving lidocaine intravenously. If one compares the increase in intracranial pressure after the first laryngoscopy in the topically treated group with the increase observed after the

only laryngoscopy in the intravenously treated group, it appears that there are only minor, insignificant differences between them (see Fig. 1 in reference 15).

The same objections may be raised in the report by Youngberg et al. (16), who concluded from a study very similar to that of Hamill et al. (15) that neither intravenous nor topical administration of lidocaine are completely effective in preventing hypertension and tachycardia induced by laryngoscopy and intubation. No obvious beneficial effect of lidocaine is seen from their data when comparisons are made between responses to the first laryngoscopy in the topically treated group and to the only laryngoscopy in the intravenously treated group (Figs. 1 and 2 in reference 16).

Finally, Hartigan et al. (17) evaluated the effect of intravenous lidocaine on the response to blind nasotracheal intubation, i.e., without laryngoscopy, in four groups of patients receiving either no pretreatment; intravenous lidocaine, 1.5 mg/kg; 0.25% phenylephrine nasal spray; or 10% lidocaine nasal spray. They found that after intubation, mean arterial blood pressure and heart rate were greatest in the group receiving lidocaine intravenously.

The increases observed in our study in mean arterial blood pressure, heart rate, and the RPP paralleled those known to take place during elective induction (3-5,26), but were more pronounced, possibly because of the time factors involved in rapid sequence induction (18,28,29). It is noteworthy that RPP in all of our patients (women), without known heart or lung diseases, reached values above 12,000, and in 11 of 16 (69%) were above 15,000, i.e., levels associated with the occurrence of ischemic episodes during anesthetic induction and intubation in a substantial number of patients with coronary artery disease (8,19). The pronounced depression of LVEF in the presence of a presumably increased sympathetic activity during laryngoscopy and intubation has previously been observed in both normal patients (5,18) and in patients with coronary artery disease, in the latter with a tendency for a prolonged depression in several patients (6). The reason for this depression is not fully understood. It can hardly be attributed exclusively to the increase in afterload evoked by laryngoscopy, because the decrease in LVEF preceded the increase in afterload (Fig. 1), suggesting a negative inotropic effect of thiopental (5,18).

From the literature it seems that there is little evidence sustaining the hypothesis that lidocaine provides protection against the tachycardic and hypertensive response to laryngoscopy and intubation. This impression was further confirmed by our own results. In not one patient receiving lidocaine were either these changes or depression of left ventricular ejection frac-

tion effectively prevented. Indeed, the curves in the two groups (Fig. 1) are virtually congruent.

Could our failure in detecting any effect of lidocaine be a result of our study design? Are, for instance, patients without heart disease more resistant to intravenous lidocaine (and diazepam and thiopental) than patients with diseased hearts (11,12,14)? Should we have given a higher dose of lidocaine, or should we have performed the intubation at some other point of time? We can not answer these questions in a completely satisfactory way. We can merely state that we chose to examine patients without heart disease to ensure they had intact circulatory responses not blunted by any drugs affecting the autonomic nerve system. In addition, we decided to use the same dose of lidocaine (1.5 mg/kg) that others have found to be effective (12-15), and we chose 2 min as time interval from IV injection of lidocaine to laryngoscopy and intubation, i.e., the average of the cited time intervals, ranging between 1 and 3 min (12-15). Finally, we conclude that in patients without heart or lung diseases, lidocaine, 1.5 mg/kg IV, administered during rapid sequence induction 2 min prior to laryngoscopy and orotracheal intubation, does not prevent or significantly blunt any of the hemodynamic reactions evoked by rapid sequence induction and intubation.

References

1. Burstein CL, LoPinto FJ, Newman W. Electrocardiographic studies during endotracheal intubation. I. Effects during usual routine technics. *Anesthesiology* 1950;11:224-37.
2. King BD, Harris LC, Greifenstein FE, Elder JD, Dripps RD. Reflex circulatory responses to direct laryngoscopy and tracheal intubation performed during general anesthesia. *Anesthesiology* 1951;12:556-66.
3. Takeshima K, Noda K, Higaki M. Cardiovascular response to rapid anesthesia induction and endotracheal intubation. *Anesth Analg* 1964;43:201-8.
4. Forbes AM, Dally FG. Acute hypertension during induction of anaesthesia and endotracheal intubation in normotensive man. *Br J Anaesth* 1970;42:618-24.
5. Chraemmer-Jørgensen B, Høilund-Carlsen PF, Marving J, Pedersen JF. Left ventricular performance monitored by radionuclide cardiography during induction of anesthesia. *Anesthesiology* 1985;62:278-86.
6. Giles RW, Berger HJ, Barash PG et al. Continuous monitoring of left ventricular performance with the computerized nuclear probe during laryngoscopy and intubation before coronary artery bypass surgery. *Am J Cardiol* 1982;50:735-41.
7. Fox EJ, Sklar GS, Hill CH, Villanueva R, King BD. Complications related to the pressor response to endotracheal intubation. *Anesthesiology* 1977;47:524-5.
8. Roy WL, Edelist G, Gilbert B. Myocardial ischemia during non-cardiac surgical procedures in patients with coronary-artery disease. *Anesthesiology* 1979;51:393-7.
9. Slogoff S, Keats AS. Does perioperative myocardial ischemia

- lead to postoperative myocardial infarction? *Anesthesiology* 1985;62:107-14.
10. Tsementzis SA, Hitchcock ER. Outcome from "rescue clipping" of ruptured intracranial aneurysms during induction anaesthesia and endotracheal intubation. *J Neurol Neurosurg Psychiatr* 1985;48:160-3.
 11. Denlinger JK, Ellison N, Ominsky AJ. Effects of intratracheal lidocaine on circulatory responses to tracheal intubation. *Anesthesiology* 1974;41:409-12.
 12. Abou-Madi MN, Keszler H, Yacoub JM. Cardiovascular reactions to laryngoscopy and tracheal intubation following small and large intravenous doses of lidocaine. *Can Anaesth Soc J* 1977;24:12-9.
 13. Stoelting RK. Circulatory changes during direct laryngoscopy and tracheal intubation: influence of duration of laryngoscopy with or without prior lidocaine. *Anesthesiology* 1977;47:381-3.
 14. Stoelting RK. Blood pressure and heart rate changes during shortduration laryngoscopy for tracheal intubation: influence of viscous or intravenous lidocaine. *Anesth Analg* 1978;57:197-9.
 15. Hamill JF, Bedford RF, Weaver DC, Colohan AR. Lidocaine before endotracheal intubation: intravenous or laryngotracheal? *Anesthesiology* 1981;55:578-81.
 16. Youngberg JA, Graybar G, Hutchings D. Comparison of intravenous and topical lidocaine in attenuating the cardiovascular responses to endotracheal intubation. *South Med J* 1983;76:1122-4.
 17. Hartigan ML, Cleary JL, Gross JB, Schaffer DW. A comparison of pretreatment regimens for minimizing the haemodynamic response to blind nasotracheal intubation. *Can Anaesth Soc J* 1984;31:497-502.
 18. Chraemmer-Jørgensen B, Høilund-Carlsen PF, Marving J, Christensen V. Left ventricular ejection fraction during anaesthesia induction: comparison of rapid sequence and elective induction. *Can Anaesth Soc J*, in press.
 19. Kaplan JA. Hemodynamic monitoring. In: Kaplan JA, ed. *Cardiac anesthesia*. New York: Grune and Stratton, Inc., 1979:109.
 20. Callahan RJ, Froehlich JM, McKusick KA, Leppo J, Strauss HW. A modified method for the in vivo labeling of red blood cells with Tc-99m: concise communication. *J Nucl Med* 1982;23:315-8.
 21. Høilund-Carlsen PF, Marving J, Jensen G. Accuracy of left ventricular ejection fraction determined by the nuclear stethoscope. *Int J Cardiol* 1982;2:237-46.
 22. Rahe AJ. Tables of critical values for the Pratt matched pair signed rank statistic. *J Am Stat Assoc* 1974;69:368-73.
 23. Tomori Z, Widdicombe JG. Muscular bronchomotor and cardiovascular reflexes elicited by mechanical stimulation of the respiratory tract. *J Physiol* 1969;200:25-49.
 24. Russell WJ, Morris RG, Frewin DB, Drew SE. Changes in plasma catecholamine concentrations during endotracheal intubation. *Br J Anaesth* 1981;53:837-9.
 25. Nigrovic V, McCulloch LS, Wajskol A, Levin TA, Martin JT. Succinylcholine-induced increases in plasma catecholamine levels in humans. *Anesth Analg* 1983;62:627-32.
 26. Cummings MF, Russell WJ, Frewin DB, Jonsson JR. The effects of suxamethonium and *d*-tubocurarine on the pressor and plasma catecholamine responses to tracheal intubation. *Anaesth Intens Care* 1983;11:103-6.
 27. Cummings MF, Russell WJ, Frewin DB. Effects of pancuronium and alcuronium on the changes in arterial pressure and plasma catecholamine concentrations during tracheal intubation. *Br J Anaesth* 1983;55:619-23.
 28. Cork RC, Weiss JL, Hameroff SR, Beatley J. Fentanyl preloading for rapid-sequence induction of anesthesia. *Anesth Analg* 1984;63:60-4.
 29. Safwat AM, Fung DL, Bilton DS. The use of propranolol in rapid sequence anesthetic induction: optimal time interval for pretreatment. *Can Anaesth Soc J* 1984;31:638-41.

Spontaneous Recovery of Neuromuscular Function after Atracurium in Pediatric Patients

Olli A. Meretoja, MD, and Ilkka Kalli, MD

MERETOJA OA, KALLI I. Spontaneous recovery of neuromuscular function after atracurium in pediatric patients. *Anesth Analg* 1986;65:1042-6.

Spontaneous recovery of neuromuscular function after a bolus dose of 0.40 mg/kg atracurium was assessed in 60 newborn to adolescent patients during balanced anesthesia. Each patient was allowed to recover spontaneously until complete recovery of the single twitch (T_1) response and the train-of-four ratio measured from the hypothenar muscle evoked compound EMG. The recovery times of T_1 from the onset of relaxation to 10% recovery and to 100% recovery

were significantly longer in patients under 10 kg of body weight than in the heavier patients (25 and 56 min vs 19 and 45 min, respectively, $P < 0.01$). The rate of recovery, calculated as the recovery index (time between 25% recovery and 75% recovery of T_1), was significantly longer in patients under 2 months of age than in older infants or children and adolescents. Atracurium remains, nevertheless, a relaxant of intermediate duration of action even in small infants.

Key Words: NEUROMUSCULAR RELAXANTS—
atracurium. ANESTHESIA—pediatric.

Atracurium has been shown to be a virtually non-cumulative neuromuscular blocking agent of intermediate duration of action in adults (1,2) and children over 2 yr of age (3,4). Goudsouzian (5) and Crumrine et al. (6) have demonstrated that the maturation of neuromuscular transmission occurs in infants within the first 2 or 3 postnatal months. Before this age infants and neonates are hypersensitive to long-acting neuromuscular blocking agents (7,8). The duration of action of metabolized relaxants is also prolonged in infants because of decreased rates of elimination (8,9). We carried out the present study to evaluate the differences, if any, that occur during spontaneous recovery of neuromuscular block induced by 0.40 mg/kg of atracurium and that are due to the age or weight of the patient.

Patients and Methods

Sixty patients, from newborns to adolescents, were selected for the study and divided into subgroups on the basis of body weight. Six groups of 10 patients were formed: those under 5 kg, 5 kg or more but less than 10 kg, 10 kg or more but less than 15 kg, 15 kg or more but less than 20 kg, 20 kg or more but less

than 30 kg, and those of 30 kg or more. Patients' data and diagnoses are shown in Tables 1 and 2. No patient had any condition known to affect the neuromuscular function. The study protocol was approved by the Ethical Committee of the Children's Hospital.

The patients over 5 kg were premedicated with oral flunitrazepam, 0.1 mg/kg (maximum dose 2.0 mg), supplemented, when indicated, with rectal methohexital, 10 mg/kg, which was the only premedication for infants under 5 kg of body weight. ECG and oscillometric blood pressure monitoring was initiated on arrival at the operating theater. Fentanyl, 3 μ g/kg together with thiopentone, 1-2 mg/kg, was administered while the patient breathed N_2O/O_2 , 2:1. Surface electrodes were placed over the ulnar nerve on the wrist to stimulate the nerve supramaximally at 20-sec intervals with a 2-Hz train-of-four stimulus, and over the hypothenar muscles to record the evoked compound electromyogram (Anesthesia and Brain function Monitor, Datex, Helsinki, Finland).

After baseline recording and calibration of the neuromuscular stimulator, 0.40 mg/kg of atracurium was injected. During anesthesia the patient was ventilated with N_2O in O_2 2:1 to maintain end-tidal CO_2 at 5.0-5.5% (Normocap, Datex, Finland). Central body temperature was maintained between 36.0 and 37.0°C. No inhalation anesthetics were used at any time, but fentanyl was administered as indicated.

Each patient was allowed to recover spontaneously to full restoration of both the single twitch (T_1) re-

* Received from the Department of Anesthesia, Children's Hospital, University of Helsinki, Helsinki, Finland. Accepted for publication May 29, 1986.

Address correspondence to Dr. Meretoja, Department of Anesthesia, Children's Hospital, SF-00290 Helsinki, Finland.

Table 1. Patient Characteristics

Group	Weight (kg)	Age (yr)	BSA (m ²)	Dose (mg/m ²)
< 5 kg	3.7 ± 0.4	0.2 ± 0.1	0.24 ± 0.02	6.0 ± 0.2
<10 kg	7.7 ± 0.4	0.7 ± 0.1	0.40 ± 0.02	7.6 ± 0.1
<15 kg	12.9 ± 0.5	2.6 ± 0.3	0.58 ± 0.02	8.8 ± 0.1
<20 kg	17.3 ± 0.6	4.8 ± 0.4	0.73 ± 0.02	9.4 ± 0.1
<30 kg	24.1 ± 0.8	7.6 ± 0.8	0.92 ± 0.03	10.4 ± 0.1
≥30 kg	40.9 ± 3.4	10.4 ± 0.7	1.29 ± 0.07	12.5 ± 0.4

The values are expressed as Mean ± SEM. BSA denotes body surface area. Each group consists of 10 patients.

Table 2. The Diagnoses and Surgical Procedures

	<2 months	<1 yr	>1 yr
Intestinal atresia	2	—	—
Pyloric stenosis	2	—	—
Hernia or undescended testicles	2	2	12
Club foot	1	3	6
Other extremity procedures	—	—	8
Endoscopy	—	3	8
Congenital heart disease ^a	—	3	5
Circumcision	—	—	3

^aAtrial septal defect or ventricular septal defect.

sponse and the train-of-four ratio (TR). During the recovery, times from the onset of neuromuscular block to 10% recovery level (T₁-10) and 100% recovery level (T₁-100) of the single twitch were measured, as well as times between 25% recovery and 75% recovery (T₁ 25-75, the recovery index). The train-of-four ratios were measured at similar times. T₄-100, the time from the onset of neuromuscular block to the maximum recovery of the fourth twitch (T₄) of the train-of-four series, was also measured.

Data are presented as means plus SEM. The statistical significance of difference among the groups' mean values was determined using the analysis of variance and the *t*-test with Welch's modification for the degrees of freedom. Linear regression analysis, with logarithmic transformation in appropriate cases, was used to determine the significance of correlations within the patient population. *P* < 0.05 was considered statistically significant.

Results

Calibration of the neuromuscular monitor prior to the administration of atracurium revealed TR values of 99 ± 1% in patients under 5 kg of body weight, whereas in heavier patients the TR was always 100%. During the most profound neuromuscular block after atracurium, the lowest single twitch height was 1 ± 1% of the calibration value in patients under 10 kg and 3 ± 1% in patients over 10 kg. 65% of the patients

under 10 kg had a block of >98%, whereas only 32% of the patients over 10 kg had a block of >98% (*P* < 0.05).

Complete recovery from the neuromuscular block was observed in all patients. However, one newborn (1.2 kg) had full recovery of only the response to a single twitch, the TR remaining at a 40% level. The average maximum recovery of the TR among the other nine patients under 5 kg was 92 ± 2% when measured for at least 5 min of constant responses. All other patients had 100% spontaneous recovery of TR.

The recovery times of the single twitch to 10% (T₁-10) and to 100% (T₁-100) were significantly longer in patients under 10 kg of body weight than in those over 10 kg (Table 3). It took 7-11 min for the fourth twitch to recover maximally after the first twitch had reached the 100% level (Table 3).

The recovery index was 14.2 ± 1.8 min in patients under 5 kg, compared to 10.3 ± 0.3 min in patients weighing more than 10 kg (*P* < 0.01). The average recovery index in infants under two months of age (weight 3.4 ± 0.5 kg) was 16.0 ± 2.1 min; this is significantly greater than the 11.1 ± 0.8 min of the infants four months of age or older (weight 6.9 ± 0.6 kg). The correlation between the logarithm of age of the infant and the recovery index was highly significant (*n* = 18, *r* = -0.670, *P* < 0.01).

Figure 1 expresses the relationship between the T₁ and the mean TR during the spontaneous recovery from atracurium-induced neuromuscular block among the different patient groups. It can be seen that in infants under 10 kg (*n* = 19) the ratio between TR recovery and T₁ recovery is greater than in heavier patients. If all of our patients are taken together, TR was 80 ± 1% of normal at the time of full recovery of the single twitch.

Discussion

The purpose of the present study was to determine, in pediatric patients during balanced anesthesia, whether the age or body weight has an effect on the recovery of neuromuscular function after injection of 0.40 mg/kg of atracurium, which is close to 1.5 times

Table 3. Spontaneous Recovery after a Bolus Dose of 0.40 mg/kg of Atracurium in Pediatric Patients

Group	T ₁ -10 (min)	T ₁ -100 (min)	T ₄ -100 (min)	T ₁ 25-75 (min)
< 5 kg	24.1 ± 4.3	56.8 ± 5.7	67.6 ± 7.6	14.2 ± 1.8
<10 kg	26.8 ± 2.3	56.1 ± 3.8	63.5 ± 3.7	11.6 ± 1.2
<15 kg	21.2 ± 2.6	46.4 ± 3.1	53.4 ± 3.3	10.5 ± 0.7
<20 kg	19.6 ± 1.7	44.4 ± 1.7	51.9 ± 1.6	10.2 ± 0.5
<30 kg	15.0 ± 2.7	39.6 ± 3.2	47.9 ± 3.8	10.2 ± 0.7
≥30 kg	21.3 ± 1.7	48.5 ± 1.2	56.6 ± 1.3	10.2 ± 0.6
P value	< 0.01	< 0.001	< 0.001	< 0.01

T₁-10, T₁-100, and T₄-100 denote the spontaneous recovery times from the onset of relaxation to the respective T₁ and T₄ levels. T₁ 25-75 denotes the recovery index.

The values are expressed as means ± SEM. P values denote the level of statistical significance when the patients under 10 kg of body weight (*n* = 20) are compared with patients over 10 kg of body weight (*n* = 40).

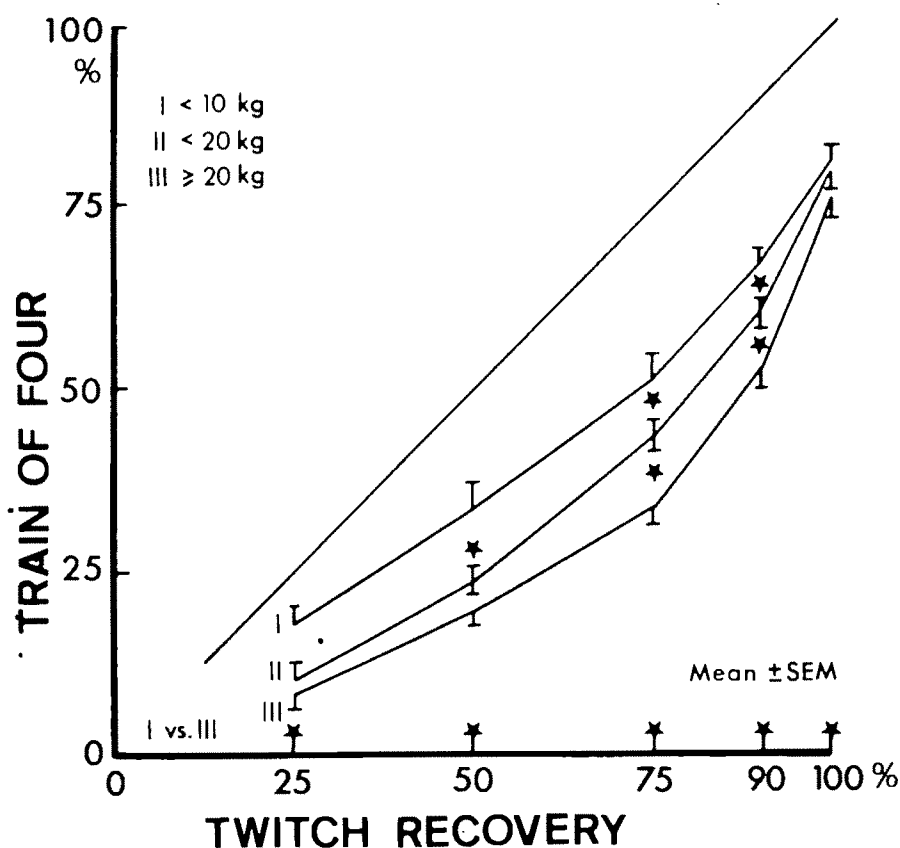


Figure 1. The relation between the single twitch recovery and the train-of-four ratio during the complete spontaneous recovery from the neuromuscular block induced by atracurium. Asterisks denote statistically significant differences between the patient groups. The line of identity has been drawn.

the ED₉₅ in children and adults (1,4,10-12). We considered it most important to achieve complete spontaneous recovery of the neuromuscular block in every patient in whom we initiated the study protocol, because possible prolongation of neuromuscular recovery does not become apparent if one antagonizes the residual neuromuscular blockade at the end of surgery. Accordingly, in most patients full neuromuscular recovery occurred after completion of the surgical procedure, though in some patients the operation started after full neuromuscular recovery.

The duration of action of atracurium in pediatric patients has previously been assessed by two study

groups (3,4,12,13). Brandom et al. found that after 0.40 mg/kg atracurium the time to the single twitch recovery of 95% was 40 min in children and 41 min in adolescents (4). These figures are almost identical to our findings in patients over 2 yr of age (41.3 ± 1.1 min). Figure 2 expresses the mean recovery times of the single twitch in patients more than and less than 1 yr of age. The longer duration of effect in infants and neonates may be a consequence of the fact that the 0.40-mg/kg dose of atracurium resulted in more profound neuromuscular block in patients under 10 kg of body weight than it did in heavier patients. However, there are no data available con-

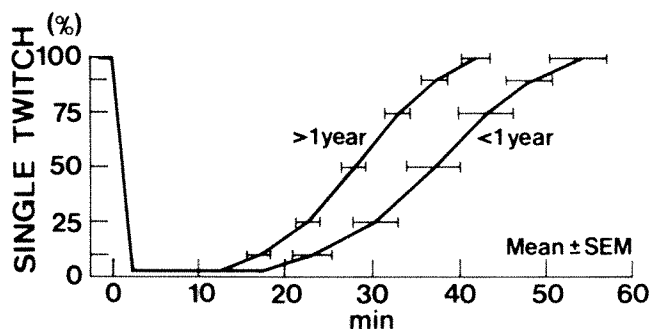


Figure 2. The time-related complete spontaneous recovery of the single twitch after 0.40 mg/kg atracurium in patients under and over 1 yr of age. The recovery times differ significantly at each time of measurement ($P < 0.01$).

cerning the ED_{95} of atracurium in infants during balanced anesthesia. Because the dose used in the present study differs when calculated not on the basis of weight of the patient but instead on the basis of body surface area (Table 1), the dose might have been severalfold ED_{95} in infants than in older patients. In clinical practice, 0.40 mg/kg atracurium produces a neuromuscular block that lasts 10 min longer in infants than in older pediatric patients (Fig. 2).

The rate of spontaneous recovery, calculated as the recovery index, was significantly longer in patients under 5 kg of body weight than in patients over 10 kg. It is unlikely that this difference was due to the fixed dose of atracurium used, because the dose of atracurium affects only the duration of the neuromuscular block, and not the recovery index (2,11). It is also improbable that the difference was due to the delayed plasma clearance of atracurium in small infants, because atracurium undergoes major elimination by spontaneous degradation and by nonspecific esterases (14).

The most probable cause of the observed prolongation of the recovery index in neonates and small infants is an increased sensitivity of these patients to the nondepolarizing neuromuscular blocking agent as a result of the relative immaturity of the neuromuscular transmission (5,6). The younger the infant, the more important age was as a determinant of the prolongation of the recovery index, and the most prolonged indexes were detected in patients under 2 months of age. Throughout the study, special care was taken to maintain the body temperature, end-tidal CO_2 , and circulation as steady as possible in all patients. Although every patient had complete spontaneous recovery of the single twitch, patients under 5 kg of body weight had an average of only 92% recovery of the train-of-four ratio. This has been demonstrated by Goudsouzian as one indication of the immaturity of the neuromuscular transmission in neonates (5).

The time between the end of surgical relaxation (T_1 10%) to 100% recovery of T_1 was fairly constantly 2.5 times the recovery index in all patient groups. This means that the rate of recovery of the single twitch in neonates and small infants is 50% longer than in children and adolescents. Fisher and Miller have shown that after a 0.070 mg/kg vecuronium, the recovery index in infants (mean age 5 months) was more than twice the recovery index in children (15). However, more extensive comparison between the recovery patterns of vecuronium and atracurium is needed before definitive differences can be proven. The average 10.3 min recovery index noted in our patients over 10 kg is consistent with results in studies carried out on children and adolescents (3-4,12), and is of the same magnitude as is found in adults (1-2).

The relationship between the train-of-four ratio and the single twitch response has not been well-studied. Only Goudsouzian et al. have determined the correlation between TR and T_1 in pediatric patients recovering from atracurium-induced neuromuscular blockade (3,12). They found a highly significant correlation to exist in both infants and children, which is corroborated by our findings when we use a linear regression analysis. In the present study, however, the relation between TR and T_1 was not found to be linear (Fig. 1). Our results showed that the smaller the patient, the better TR increases in proportion to the recovery of T_1 . Although the physiologic explanation for this finding remains obscure, it is of clinical importance when we consider the narrow reserves of muscular strength in infants. Infants may derive benefit when atracurium is used as their neuromuscular blocking agent.

In summary, 0.40 mg/kg atracurium produced neuromuscular blockade that lasted 30% longer in infants than in older pediatric patients. The recovery index was especially prolonged in patients under 2 months of age, in whom the recovery index was 50% greater than in older children and adolescents. The train-of-four ratio, however, recovers more in relation to recovery of the single twitch response in infants than it does in older children or adolescents.

References

1. Basta SJ, Ali HH, Savarese JJ, et al. Clinical pharmacology of atracurium besylate (BW 33A): a new non-depolarizing muscle relaxant. *Anesth Analg* 1982;61:723-9.
2. Ali HH, Savarese JJ, Basta SJ, Sunder N, Gionfriddo M. Evaluation of cumulative properties of three new non-depolarizing neuromuscular blocking drugs BW A444U, atracurium and vecuronium. *Br J Anaesth* 1983;55:1075-111S.
3. Goudsouzian NG, Liu LMP, Cote CJ, Gionfriddo M, Rudd GD. Safety and efficacy of atracurium in adolescents and children anesthetized with halothane. *Anesthesiology* 1983;59:459-62.
4. Brandom BW, Rudd GD, Cook DR. Clinical pharmacology of atracurium in pediatric patients. *Br J Anaesth* 1983;55:117S-121S.

5. Goudsouzian NG. Maturation of neuromuscular transmission in the infant. *Br J Anaesth* 1980;52:205-13.
6. Crumrine RS, Yodlowski EH. Assessment of neuromuscular function in infants. *Anesthesiology* 1981;54:29-32.
7. Long G, Bachman L. Neuromuscular blockade by *d*-tubocurarine in children. *Anesthesiology* 1967;28:723-9.
8. Fisher DM, O'Keeffe C, Stanski DR, Cronelly R, Miller RD, Gregory GA. Pharmacokinetics and pharmacodynamics of *d*-tubocurarine in infants, children and adults. *Anesthesiology* 1982;57:203-8.
9. Matteo RS, Lieberman IG, Salanitro E, McDaniel DD, Diaz J. Distribution, elimination, and action of *d*-tubocurarine in neonates, infants, children, and adults. *Anesth Analg* 1984;63:799-804.
10. Gramstad L, Lilleaasen P. Dose-response relation for atracurium, ORG NC45 and pancuronium. *Br J Anaesth* 1982;54:647-50.
11. Sokoll MD, Gergis SD, Mehta M, Ali NM, Lineberry C. Safety and efficacy of atracurium (BW33A) in surgical patients receiving balanced or isoflurane anesthesia. *Anesthesiology* 1983;58:450-5.
12. Goudsouzian N, Liu LMP, Gionfriddo M, Rudd GD. Neuromuscular effects of atracurium in infants and children. *Anesthesiology* 1985;62:75-9.
13. Brandom BW, Woelfel SK, Cook DR, Fehr BL, Rudd GD. Clinical pharmacology of atracurium in infants. *Anesth Analg* 1984;63:309-12.
14. Hughes R, Chapple DJ. The pharmacology of atracurium: a new competitive neuromuscular blocking agent. *Br J Anaesth* 1981;53:31-44.
15. Fisher DM, Miller RD. Neuromuscular effects of vecuronium (ORG NC 45) in infants and children during N₂O, halothane anesthesia. *Anesthesiology* 1983;58:519-23.

Failure of the Tourniquet-Twitch Test as a Diagnostic or Screening Test for Malignant Hyperthermia

Beverley A. Britt, MD, FRCP(C), Elizabeth A. Scott, MSc, Asia Kleiman, MD,
Philip Jones, MD, and David J. Steward, MD, FRCP(C)

BRITT BA, SCOTT EA, KLEIMAN A, JONES P, STEWARD DJ. Failure of the tourniquet-twitch test as a diagnostic or screening test for malignant hyperthermia. *Anesth Analg* 1986;65:1047-50.

We have performed the tourniquet-twitch test of Roberts and Ryan in normal and in malignant hyperthermia (MH) patients and relatives. This test measures the ratio of electrically induced thumb twitches noted after 10 min of ischemia with those noted immediately prior to the ischemia. We found no significant differences in this ratio between normal subjects and those who have had MH reactions, or relatives of such individuals. Furthermore, we have observed

no significant differences in tourniquet-twitch ratios between those with normal caffeine-halothane contractures and persons with caffeine-halothane contractures tests positive for MH. These findings do not agree with those of Roberts and Ryan, who reported that tourniquet-twitch ratios were higher in MH patients than in normal patients. We have, however, determined that subjects with tourniquet-twitch ratios ≥ 1.8 are substantially younger than those with tourniquet-twitch ratios ≤ 1.0 . Therefore we do not believe that the tourniquet-twitch test is useful as a diagnostic, or even as a screening test for MH.

Key Words: HYPERTHERMIA—malignant.

At present, accurate diagnosis of malignant hyperthermia (MH) requires a skeletal muscle biopsy in order to obtain muscle for performance of the caffeine-halothane contracture (CHC) test (1). Many patients are reluctant to undergo such an invasive procedure. Moreover, the time, expense and expertise required preclude use of a skeletal muscle biopsy for diagnosis of large kindreds or for screening the general population. A great need exists, therefore, to develop a simple, rapid, inexpensive and noninvasive test to diagnose, or at least screen for, the MH trait.

Roberts et al. have recently described such a test, the tourniquet-twitch (TT) test (2). During this test, the amplitude of electrically-induced thumb twitches is measured before, during, and after inflation of an upper arm tourniquet. The ratio of the maximum twitch tension during the first 4 postinflation min to the maximum twitch tension immediately before cuff inflation is then calculated. Ratios less than 1.0 are considered to be normal, whereas ratios greater than 1.0 are considered by these authors to be indicative of the MH trait.

Roberts et al. have not, however, satisfactorily correlated this test with any recognized diagnostic test for MH. We have therefore performed the TT test in 282 patients who have also been evaluated using the caffeine-halothane contracture test (1).

Methods

Informed consent was obtained from all 282 patients in accordance with the Human Experimentation Committee of the University of Toronto.

Tourniquet-Twitch Test

Supramaximal square wave pulses at a frequency of 0.1 Hz were applied from a Grass S88 stimulator to the ulnar nerve at the wrist, thus producing thumb adduction. The twitches were recorded on a Grass Model 7 Polygraph via a Grass FT 10 force displacement transducer. Recordings were made continuously before, during, and after a 10-min period of ischemia of the upper limb, produced by inflation of a tourniquet to 250–300 mm Hg. The TT ratio was calculated as described in the introductory section of this paper. A "normal" or "negative" response was considered to be a gradual increase in twitch amplitude (of as much as 60%) during the ischemic period,

Received from the Departments of Anaesthesia and Pharmacology, University of Toronto, Toronto, Ontario, Canada. Accepted for publication April 25, 1986.

Address correspondence to Dr. Britt, Department of Anaesthesia, Toronto General Hospital, 101 College Street, Room CCRW 2-835, Toronto, Ontario M5G 1L7, Canada.

"Normal" Tourniquet Twitch Test

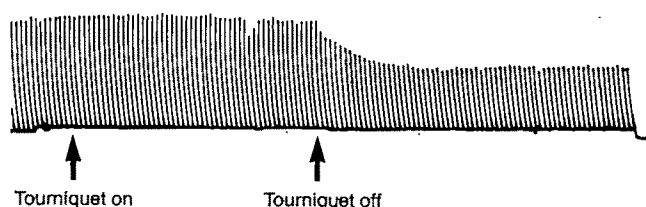


Figure 1. "Normal" tourniquet-twitch test—a gradual increase in twitch amplitude during period of ischemia; a decrease in amplitude to below ischemic value during first 1 or 2 min after release of cuff and, finally, a gradual increase during the next 1–3 min approximately to the original twitch height.

"Positive" Tourniquet Twitch Test

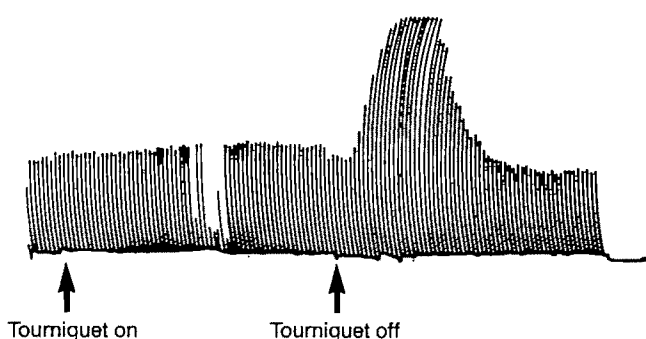


Figure 2. "Positive" tourniquet-twitch test—a gradual increase in twitch amplitude during period of ischemia; a transient decrease in twitch amplitude after release of cuff; followed by an increase in twitch amplitude, for 3–4 min, to a height greater than the maximum seen during ischemia; and, finally, a decrease in twitch amplitude approximately to the original twitch height.

followed by a decrease in amplitude (to below the preischemic value) during the first 1–2 min after release of the tourniquet, and finally a gradual increase (during the next 1–3 min) to approximately, or a little less than, the original twitch height (Fig. 1). A "positive" response differed from the above in that after the postischemia decrease in twitch height and within the first 2 min after tourniquet, the amplitude increased for 3–4 min to a height greater than maximum observed during ischemia, and then gradually declined to approximately, or a little more than, the original twitch height (Fig. 2). An "equivocal" response was similar to the positive response, except that the peak postischemia twitch height failed to exceed that occurring during ischemia (Fig. 3).

Caffeine-Halothane Contracture Test

The CHC test was performed by the method previously described by us (1,3,4). The mM of caffeine required to raise the resting tension of isolated skeletal

"Equivocal" Tourniquet Twitch Test

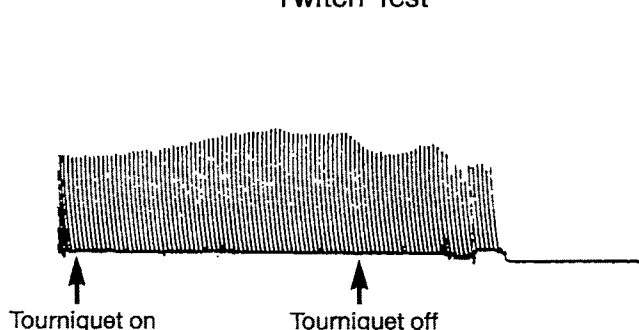


Figure 3. "Equivocal" tourniquet-twitch test—a gradual increase in twitch amplitude during period of ischemia; a transient decrease in twitch amplitude after release of the cuff; followed by a brief increase in twitch amplitude to a height less than maximum observed during ischemia; and, finally, a decrease in twitch amplitude approximately to the original twitch height.

Table 1. Tourniquet-Twitch Test Ratios: Normal Controls vs MH Patients and MH and Normal Relatives

	0	1	2	3	4	5–10	Control
n	71	92	37	17	23	20	22
Mean	1.23	1.26	1.43	1.33	1.18	1.49	0.59
SEM	0.06	0.06	0.12	0.10	0.07	0.16	0.07
Student's <i>t</i> -test	1.29*	1.41*	2.09 ^b	2.03*	0.97*	2.34 ^b	

Relatives: 0, = MH patients who had had one or more previous reactions characterized by fever, rigidity, tachycardia and metabolic acidosis; 1, first degree relatives of an MH patient, i.e., sibling, parent, or offspring; 2, second degree relatives of an MH patient, i.e., niece, nephew, aunt, uncle, grandparent, or grandchild; 3, third degree relatives of an MH patient, i.e., first cousin, grand-niece, grand-nephew, great aunt, great uncle, great grandparent, or great grandchild; 4, fourth degree relatives of an MH patient, i.e., second cousins (other types of relatives were either dead or not yet born); 5, fifth degree relatives of an MHS patient, i.e., third cousins, etc., to tenth degree relatives.

Mean, mean arithmetic twitch tension ratio.

*Not significant ($P > 0.05$).

^b $P < 0.05$.

muscle fascicles by 1.0 g in the absence of the halothane was termed the "caffeine specific concentration" (CSC). The mM of caffeine required to increase the resting tension of isolated skeletal muscle fascicles by 1.0 g in the presence of 1.0 vol% halothane was termed the "caffeine specific concentration—halothane" (CSC-H).

Classification of Data

Subjects were classified according to the following: 1) closeness of relationship to individuals who had MH reactions (71 malignant hyperthermia susceptible (MHS) probands, 189 MHS relatives and 22 controls) and 2) according to their CHC test results performed as described in reference 4 and in table legends of

Table 2. Tourniquet-Twitch Test Ratios: Normal Controls vs MH Patients and MH Relatives with Various Combinations of Caffeine-Halothane Contracture Tests Positive for Malignant Hyperthermia

	HCK + HK (All patients +ve with halothane)	HCK + CK + C (All patients +ve with caffeine)	HCK + HK + CK + C (All +ve patients except type K)	HCK + HK + CK + C + K (All +ve patients)	Control
<i>n</i>	31	92	97	193	22
Mean	1.30	1.25	1.25	1.29	1.08
SEM	0.09	0.06	0.06	0.04	0.07
Student's <i>t</i> -test	1.82 ^a	1.28 ^a	1.33 ^a	1.65 ^a	—

H, patients with contractures in the presence of halothane alone; C, lower than normal CSC (mild MH); K, patients with lower than normal CSC-Hs, i.e., patients with greater than normal responses only in the combined presence of caffeine plus halothane (the most mild variant of MH); +ve with halothane, contracture of a muscle fascicle in the presence of halothane alone; +ve with caffeine, lower than normal CSC. Mean, mean arithmetic twitch tension ratio.

^aNot significant ($P > 0.05$).

Table 3. Comparison of Tourniquet-Twitch Ratios of <1.0 with Those of ≥ 1.8

	Tourniquet Twitch Ratios		Student's <i>t</i> -test
	<1.0	>1.8	
Halothane Contractures (H)			
<i>n</i>	54	37	
Mean	0.08	0.22	− 1.31 ^a
SEM	0.05	0.10	
Caffeine specific concentration (CSC)			
<i>n</i>	54	37	
Mean	4.68	5.72	− 1.56 ^a
SEM	0.33	0.63	
Caffeine specific concentration in presence of 1.0% halothane (CSC-H)			
<i>n</i>	54	37	
Mean	1.06	1.10	− 0.23 ^a
SEM	0.11	0.16	
Age			
<i>n</i>	54	37	
Mean	34.59	21.76	4.68 ^b
SEM	1.62	2.24	

Mean, mean arithmetic twitch tension ratio.

^aNot significant ($P > 0.05$).

^b $P < 0.001$.

this paper (193 MHS probands and MHS relatives who had biopsies positive for MH and 22 control subjects).

Statistical Analysis

The data were compared by means of two sample Student's *t*-tests.

Results

There were almost no significant differences in the TT ratios between normal control subjects and MH patients, or between normal controls and first to tenth

degree relatives of MH patients (Table 1). Similarly, there were almost no significant differences between control subjects and MH patients and relatives or MH patients whose biopsies were positive. Thus no significant differences were revealed by comparison of normal controls with types HCK + HK (i.e., all patients whose muscle developed contractures in the presence of halothane alone); types HCK + CK + C (i.e., all patients whose muscle, in the absence of halothane, required lower than normal doses of caffeine to develop a one gram contracture); types HCK + HK + CK + C (i.e., all patients with CHC tests positive for MH with the exception of type K); and types HCK + HK + CK + C + K (i.e., all patients with CHC tests positive for MH including type K) (Table 2).

To ascertain whether the TT test might at least be useful as a screening test, we also compared only those patients whose TT ratios were less than 1.0 with those patients whose TT ratios were greater than or equal to 1.8 (Table 3). The variables analyzed included the following: halothane contractures; dose of caffeine required to increase the resting tension of a skeletal muscle fascicle by 1.0 g in the absence of halothane; dose of caffeine required to increase the resting tension of a skeletal muscle fascicle by 1.0 g in the presence of 1.0% halothane (1,3,5); and age. Student's *t*-tests for the first three comparisons showed no significant differences (Table 3). Student's *t*-tests for age, however, revealed highly significant differences (Table 3). Thus patients with tourniquet twitch values greater than or equal to 1.8 were substantially younger than patients with tourniquet twitch ratios less than 1.0.

Discussion

The TT test is based on studies by Roberts et al. (6) in healthy non-MH human volunteers of neuromuscular function during ischemia. In nearly all their subjects the twitch tension amplitude increased slowly

throughout the period of ischemia. The cause of this step-like increase in perischemic twitch tension, the "stair-case" phenomenon, is not known but may be related to a progressive lack of oxygen in either the motor nerves at the neuromuscular junction or in the muscle cell membrane, causing excessive permeability to ions with resultant abnormal flux of calcium, along with excessive increases in lactate and corresponding decreases in pH (6).

We (7) and others (8) have observed that the duration of ischemia influences the amplitude of the postischemic twitch tension amplitude. Thus after 3-5 min of occlusion, twitch tensions decrease moderately in most subjects, remain at levels slightly below those observed prior to inflation of the tourniquet for several minutes, and then slowly return to preinflation values. After 10 min of occlusion, most subjects exhibit a reduction in twitch tensions, though a few exhibit an increase. After 20-30 min of occlusion, twitch tension also decreases transiently in most subjects after release of the cuff, followed by a fairly rapid increase in a curvilinear fashion to heights up to two or three times those observed in the preinflation period (peaking at 2 min). Then, after 3-4 min, tensions decline, again in a curvilinear fashion, to preinflation levels. Thus the longer the duration of forearm ischemia, the greater the percent of subjects subsequently exhibiting enhancement of thumb twitch tension.

Roberts et al. (8) have reported that subjects exhibiting an increase in twitch tension after only 10 min of cuff inflation have had MH reactions or are related to such persons, whereas those exhibiting a decrease in twitch tension after 10 min of cuff inflation have not had MH reactions and are not related to anyone who has had such a reaction (8). A 10-min cuff inflation period was chosen by Roberts et al. because they felt that this length of time provided the best diagnostic discrimination between normal and MH individuals.

However, our findings are not in agreement with those of Roberts et al. with respect to the relationship between the MH trait and preincrease in twitch tension after 10 min of ischemia. We observed, as did Roberts et al., the "stair-case" phenomenon during ischemia, and the segregation of patients into two discrete groups in the postischemic period—those in whom twitch tensions increased and those in whom

they decreased. These two groups do not, however, show any positive relationship with the presence or the absence of the MH trait. Thus insignificant differences are observed when comparisons are made between those who have had MH reactions and/or their relatives controls, when comparisons are made between those with CHC tests positive for malignant hyperthermia and controls or controls plus normal relatives, or even when the latter comparisons are made excluding patients with twitch test results in the central grey area between >1.0 and <1.8 . Therefore, the tourniquet-twitch test does not appear to us to be a valid screening test for MH.

The division of the TT test values into two fairly discrete groups appears to be due at least in part to age. Younger subjects tend to exhibit increases and older patients decreases in twitch tension after release of the cuff. This age difference may account in part for the results reported by Roberts et al., as their MH probands tended to be children, whereas their volunteer controls were usually adults.

References

1. Britt BA, Frodis W, Scott E, Clements M-J, Endrenyi L. Comparison of the caffeine-skinned fibre tension (CSFT) test with the caffeine-halothane contracture (CHC) test in the diagnosis of malignant hyperthermia. *Can Anaesth Soc J* 1982;29:550-62.
2. Roberts JT, Ali HH, Ryan JF. A tourniquet test for malignant hyperthermia. Unpublished data, March, 1979.
3. Britt BA, Endrenyi L, Kalow W, Peters PL. The adenosine triphosphate (ATP) depletion test: comparison with the caffeine contracture test as a method of diagnosing malignant hyperthermia susceptibility. *Can Anaesth Soc J* 1976;23:624-35.
4. Britt BA, Scott E. Failure of the platelet-halothane nucleotide depletion test as a diagnostic or screening test for malignant hyperthermia. *Anesth Analg* 1986;65:171-5.
5. Britt BA, Kalow W, Gordon A, Humphrey JG, Rewcastle NB. Malignant hyperthermia—an investigation of five patients. *Can Anaesth Soc J* 1973;20:431-67.
6. Roberts JT, Ali HH, Mathieu A. Postischemic depression of neuromuscular function: a preliminary report. American Society of Anesthesiologists Annual Meeting, New Orleans: Abstracts of Scientific Papers, 1977:327.
7. Jones PIE, Britt BA, Steward DJ, Volgyesi GA, Scott E, Frodis W. The "tourniquet test" and malignant hyperthermia. Unpublished data.
8. Roberts JT, Ali HH, Ryan JF, Reynolds A, Sreter FA, Allen PD, Mabuchi K, Gilbert JP. Tourniquet test as a predictive screen for malignant hyperthermia. Unpublished data, 1980.

Special Article

Harold Randall Griffith, MD, CM, FRCP(C), FFARCS(ENG), FRCS(C): 1894-1985

Thomas H. Seldon, MD

Because of my many years of friendship with Dr. Harold Griffith, the Editor of *Anesthesia and Analgesia* has asked me to prepare a brief commentary highlighting Dr. Griffith's contributions to the practice of anesthesiology and his association with the International Anesthesia Research Society.

Dr. Griffith was born in Montreal, Quebec, on July 25, 1894, and spent the major portion of his life living and working within five miles of his birthplace. He graduated from the High School of Montreal in 1910 and went on to earn a Bachelor of Arts Degree from McGill University, Montreal, in 1914. He attended McGill University as a student in the Faculty of Medicine, but left during his second year to enlist in the Canadian Armed Forces during World War I.

Griffith served as a Corporal in the No. 6 Canadian Field Ambulance Corps in the Ypres area of France. His unit was ordered to take charge of a "Hospital for Self-Inflicted Wounds," which served the whole of the northern British Army area. Although his main responsibility was to tend daily to wound dressings, he would occasionally assist the surgeon with a particularly extensive debridement by pouring a few drops of chloroform on a mask held over the patient's face. This was his first experience as an anesthetist.

He was awarded the military medal for "bravery in the field" while serving at Vimy Ridge. Soon after the allies captured this strong point, he was transferred to the Royal Navy as a surgeon sublieutenant serving in the Mediterranean Theater. Here he remained for the duration of the war.

In 1918, he returned to Montreal to complete his

medical school training at McGill University, from which he graduated in 1922 with the degrees MD, CM (Doctor of Medicine and Master of Surgery). While still a student, he worked for two years as an intern at the Homeopathic Hospital, where his career in anesthesia really began. Since the hospital had no regular anesthetist, he and some of his fellow students took turns skipping classes to administer anesthetics. Ethyl chloride was usually used for a quick induction, followed by chloroform and ether. Great care and skill was necessary, since there was little, if any ancillary equipment such as gas machines, oxygen, airways, and suction.

In 1922, Dr. Griffith traveled to Philadelphia, Pennsylvania, to spend a year in post graduate study at Hahnemann Medical College, after which he received the degree of MD in homeopathic medicine. He returned to Montreal in 1923 and was appointed Anesthetist in Chief at the Homeopathic Hospital. He remained in this position until 1959. He continued to practice anesthesia until his retirement in 1966.

During World War II, Dr. Griffith was appointed a Consultant to the Royal Canadian Air Force. Early on, he recognized the great need for anesthesia personnel and helped organize a teaching program for physicians in the armed services. Later he developed the McGill Diploma Course, which consisted of weekly meetings of all the staff and residents from McGill and the University of Montreal. Here residents presented papers, staff gave lectures on the basic sciences, and guest speakers participated.

In 1946, Griffith was appointed lecturer in the newly formed Department of Anesthesia in the Faculty of Medicine at McGill, under Professor Wesley Bournè. In 1948, he was promoted to Assistant Professor and served from 1951 to 1956 as Professor and Chairman of the Department. He argued that clinical teaching

Received from Dr. Thomas H. Seldon, Rochester, Minnesota.
Accepted for publication May 29, 1986.

Address correspondence to Dr. Seldon, 211 N.W. 2nd Street,
Rochester, MN 55901.

needed to be supplemented by research opportunities to properly educate anesthetists. To this end, he persuaded Sir Henry Dale and the Wellcome Trust to support a research professorship.

In Montreal, he introduced many innovations in the practice of anesthesia—including the metal, pharyngeal airway, and later endotracheal administration of gaseous anesthetic agents—first through small catheters and then by ever improving endotracheal tubes. As new agents were developed, he included them in his practice and refined techniques of administration to improve patient comfort and safety.

Early in the 1940s, after a conversation with the late Dr. Lewis Wright of New York about a new curare extract named Intocostin, it occurred to Dr. Griffith that such a muscle relaxant might be useful as a supplement to inhalation anesthesia. In 1942, he used Intocostin in conjunction with cyclopropane anesthesia, on a young man undergoing appendectomy. The combination produced in a highly desirable condition for the surgeon and resulted in the ever-widening acceptance of muscle relaxants. At about the same time, he established the first postanesthesia recovery room in Canada. He was instrumental in the organization of the Canadian Anaesthetists Society, becoming its first president, and later serving on the Council for 20 years. Many of his interests were encouraged and stimulated by close, personal friends such as Dr. Frank McMechan, founder of the International Anesthesia Research Society in Cleveland, Ohio; Dr. Ralph Waters, Professor and Chairman of the Department of Anesthesia at the University of Wisconsin in Madison; and Dr. Wesley Bourne of Montreal.

In 1948, Dr. Griffith was invited to join the Board of Trustees of the International Anesthesia Research Society (IARS). He was already aware of the need for worldwide communication among anesthesiologists. In 1949, he was appointed Chairman of the Board of Trustees of the IARS and continued in this capacity for several years. The annual Congress of the IARS in 1951 was held in London, England, in joint session with the Association of Anaesthetists of Great Britain and Ireland. Two weeks later, the French Society held an International Congress in Paris. At both of these meetings, there was considerable discussion leading to the consensus that the advancement of anesthesia would be best served by anesthesiologists and not dominated by others. It was agreed that the worldwide organization of the specialty of anesthesiology must be controlled by anesthesiologists.

At the Paris meeting, a committee was formed to study the possibility of a world-wide organization of anesthesia societies. The committee included Dr.

Jacques Boureau of Paris, Dr. John Gillies of Edinburgh, Dr. Alex Goldblat of Brussels, Dr. Torsten Gordh of Stockholm, with Dr. Griffith as Chairman. The world was "divided" by Dr. Goldblat and Dr. Griffith, and each, by his own effort and finances, gathered all available information from his allotted portion. Thus informed, the Committee met in Brussels, Belgium in June 1953. The meeting was funded by the Council for International Organization of Medical Societies and the IARS. The IARS underwrote a considerable portion of the organizational expenses and subsequently published the Proceedings of the First Congress. The late Dr. Oscar R. Schwidetsky provided two generous financial donations, which materially helped this young federation to survive. I remember well the great enthusiasm that Harold Griffith had for this project, particularly when he was reporting to the Board of the IARS. Of the many direct or indirect contributions that Dr. Griffith made to the specialty, I feel that he got as much satisfaction from his involvement with the organization of the World Federation of Societies of Anesthesiologists as from any other.

Representatives from the Association of Anaesthetists of Great Britain and Ireland, the Netherlands Society of Anesthesiologists, the IARS, the societies of Italy and Australia, and the Canadian Society were added to the original committee. The American Society of Anesthesiologists, the largest anesthesia society in the world, chose not to join at this time. Although the IARS did not really represent anesthesia for the United States, without its support, the United States would have played essentially no part in the early growth of the World Federation of Societies of Anesthesiologists.

The organizing committee met again in 1954 in Scheveningen, The Netherlands, to further prepare for the 1955 World Congress. Again, Dr. Griffith presided. The first World Congress was held in Scheveningen on September 5-10, 1955, under the able chairmanship of Dr. Griffith, aided by Dr. Ritsema van Eck of Groningen, The Netherlands, President of the Congress.

Just prior to the opening of the Congress, Dr. Griffith was touring in Europe with a small group of friends when he developed hepatitis and required hospitalization, in Turin, Italy. In spite of a severe illness, and against his attending physician's advice, he left the hospital to go to the Congress. On the final day of the Congress, Dr. Griffith was chosen to be the first president of the World Federation of Societies of Anesthesiologists.

He suffered no apparent lasting effects from his illness, and at the Second World Congress, held in Toronto, Canada in 1960, he declined the nomination

for a second term as President and retired from membership on the Executive Committee. He did, however, accept the honor of being named Founder President of the World Federation.

Dr. Griffith's wife, née Linda Aylen, now lives in an attractive and comfortable retirement home in Montreal. Two daughters, Linda Mary Jacobson and Barbara Clark, five grandsons, and one granddaughter also survive. I enjoyed Harold's many stories of happy vacations in their Laurentian mountain summer home where he and his wife shared in the fun and activities of their grandchildren.

We all recognize Harold Griffith as a superb administrator and one of the great contributors to our specialty. His published papers are permanent records of his serious interest in teaching, research, and clinical practice. It is interesting to note that he had the unique distinction of having served in all three branches of the Canadian Armed Services—Army, Navy, and Air Force. Among the many distinguished honors he received, there were:

Feltrinelli Prize of Accademia dei Lincei, Rome, 1954

Henry Hill Hickman Medal of the Royal Society of Medicine, London, 1956

Distinguished Service Award, American Society of Anesthesiologists, 1959

Founder-President, World Federation of Societies of Anesthesiologists, 1960

Canadian Anaesthetists Society Medal, 1962

Honorary Fellowship of the Faculty of Anaesthetists of the Royal College of Surgeons of England, 1969

Ralph Waters Award, Illinois Society of Anesthesiology, 1970

Officer, Order of Canada, 1974

Honorary LLD, University of Saskatchewan, 1974.

Harold's many friends throughout the world, his peers, and countless patients who have benefited from his contributions will always be grateful for his having lived and worked among us. After two years of debilitating Parkinson's Disease, he died on May 7, 1985.

I am indebted to Dr. Douglas Craig of Winnipeg, Manitoba, to Dr. Rod Gordon of Toronto, Ontario, and to Dr. Deirdre Gillies of Montreal, Quebec, for their help in preparing this manuscript.

Review Article

Acquired Immunodeficiency Syndrome: An Overview for Anesthesiologists

Ernest R. Greene Jr, MD, PhD

The acquired immunodeficiency syndrome (AIDS) epidemic in the United States is in an exponential growth phase, the number of cases doubling each year (1). As of December 30, 1985, there were 15,948 diagnosed and reported cases and 8161 deaths. This disease, reported in all 50 states, is clearly not just a big-city problem (Centers for Disease Control, personal communication). Nor is it confined to the high-risk groups that were first identified, namely, promiscuous homosexual men, intravenous drug abusers, hemophiliacs, and recent Haitian immigrants. The Haitians have been dropped from this listing, but infants of high-risk mothers (2-4) and patients receiving multiple transfusions of blood products have been added to it (5,6). The causative agent of AIDS, the human T-lymphotropic virus type III (HTLV-III)—also known as the lymphadenopathy-associated virus (LAV)—can also be transmitted heterosexually by either sex (7-9). Most of the cases of AIDS first reported in this population were in spouses of members belonging to high-risk groups. More recently, promiscuous heterosexual behavior, including female prostitution, has received recognition as a problem in this regard. Such activity appears to be the most important means of transmission of AIDS in some countries (10-12) and is likely to become more important in the United States as well.

AIDS is an incurable, ultimately fatal disease (13,14). The full-blown disease is characterized by a severe reduction in cell-mediated immunity, caused primarily by the critical injury of helper T-lymphocytes by

the HTLV-III retrovirus. The loss of these cells leads to functional defects in virtually all aspects of the immune system (15). As a consequence, the victims of this disease are plagued by recurrent opportunistic infections of every variety (protozoan, fungal, viral, bacterial) and the development of rampant malignancies. Of the many AIDS-related diseases that are seen, *Pneumocystis carinii* pneumonia and Kaposi's sarcoma (possibly due in turn to an opportunistic infection with cytomegalovirus) are the most notorious (13). Although more or less successful therapies exist for many of these diseases, attempts to reconstitute the damaged immune system have been unsuccessful (16). Eventually, after repeated onslaughts of this relentless disease, the debilitated patient succumbs.

Not everyone infected by HTLV-III develops AIDS. Its long incubation period, known with some assurance in the case of transfusion-associated AIDS to average 29 months for adults and 14 months for infants (6) and to extend up to at least five years in some cases (17), makes it difficult to say how many infected persons will eventually develop the full-blown syndrome. Several studies have been performed in an attempt to answer this question. A typical result was the finding of a 9% progression to AIDS over a 28-month period (18). Overall, for homosexual men, studies suggest that from 5 to 20% will develop AIDS within the first 2-5 years after becoming infected with HTLV-III (19).

Among the majority of infected persons who do not develop AIDS, there is a wide spectrum of the manifestations of disease. Many remain asymptomatic or mildly symptomatic, others develop a generalized lymphadenopathy (20,21), and yet others develop an AIDS-related complex (ARC). The latter do not manifest the typical opportunistic infections and malignancies seen in AIDS, but they do have significant immunologic abnormalities. The signs and

Received from the Departments of Anesthesiology, Veterans Administration Medical Center and University of Alabama at Birmingham, Birmingham, Alabama. Accepted for publication March 26, 1986.

Address correspondence to Dr. Greene, University of Alabama at Birmingham, Department of Anesthesiology, University Station, Birmingham, Alabama 35294.

symptoms of disease that they exhibit include diffuse lymphadenopathy, weight loss, fever, chronic diarrhea, oral thrush, malaise, and lethargy (13). Progression from ARC to AIDS is not unusual; this has been observed to happen in about 20% of the cases (21).

The seriousness of the AIDS epidemic is substantially increased by the high prevalence of the HTLV-III carrier state. Because HTLV-III is a retrovirus, persistent infection is to be expected (19,22) according to the following mechanism. The virus first interacts with and then penetrates the plasma membrane of the target cell, for instance, a helper T-lymphocyte. The virus is uncoated in the cytoplasm, and its RNA is transcribed by reverse transcriptase to form proviral DNA, some of which is integrated into the host chromosomal DNA. These integrated DNA sequences in turn produce viral RNA capable of translation into viral proteins. Virions are assembled in the cell and released by budding through the plasma membrane (22,23). Once incorporated in the human genome the proviral DNA presumably remains active for the life of the infected cell. Another feature that may serve to complicate the treatment of this infection is that HTLV-III also replicates in the brain, residing in a sanctuary behind the blood-brain barrier (23-26). The resulting subacute encephalitis, seen in about one third of the patients with AIDS, leads to a progressive dementia that often terminates rapidly in coma and death (27,28). One fifth of the patients with AIDS develop vacuolar degeneration of the spinal cord with associated paraparesis, ataxia, and incontinence (28). Even if the virus kills all the primary target cells (the helper T-lymphocytes), the neural tissue may be sufficient to maintain a persistent infection. Whether virus is shed continuously or intermittently by an infected individual is yet to be determined.

When the danger of acquiring AIDS by transfusion from asymptomatic carriers (6) was recognized, the development of a capability to screen blood products became a high-priority endeavor (29). On March 2, 1985, the Food and Drug Administration licensed the first enzyme-linked immunosorbent assay (ELISA or EIA) for antibody to HTLV-III. Such an assay is now used by the American Red Cross on all units of donated blood. Of the first 1,027,786 units tested, 1723 (0.17%) were repeatedly reactive. They were designated "EIA-positive" (EIA+) and were not released for transfusion. EIA-positive units are retested to keep the number of false positives as low as possible. The main reason for this has been to avoid unnecessarily distressing blood donors by falsely labeling them possible HTLV-III carriers.

Of 1455 EIA+ units of blood that were retested

using the sensitive Western blot analysis, 333 were positive (WB+), implying a prevalence of 38 EIA+/WB+ donors per 100,000 (30). An independent estimate yielded a similar prevalence of 45 infected persons per 100,000 adults in the United States at no known risk of AIDS (31). The prevalence of HTLV-III infection is much greater when the high-risk categories are included. Estimates of the total number of persons infected in the United States range from about 400,000 to 1,800,000 (1,14,19,31).

Licensed EIA kits from several different manufacturers for screening blood products are now in use. None has 100% sensitivity, that is, none is capable of screening out 100% of the units containing HTLV-III antibody. The actual sensitivities claimed by the manufacturers range from 93.4% to 99.6% (32). Thus from 0.4% to 6.6% of the units released are only falsely negative and actually do contain HTLV-III antibody and, perhaps, the virus itself. Because a single unit of infected blood can cause AIDS (1), the probability of getting an infected, though screened, unit is of interest. If one were to assume that all the false negative units of blood released for transfusion are infected with virus, that the EIA test has an average sensitivity of 99%, and that the prevalence of EIA+ donors is 38 per 100,000, then there will be 3.8 infected units per million released. The risk that a patient will acquire the virus rises linearly with the number of units transfused. Blood products such as cryoprecipitate, which are sometimes pooled from several donors, appear to pose a greater risk as well, although heat treatment, now increasingly used, may inactivate the virus and render the product safer (33,34). Units of blood products found to be EIA-negative on the first test are not retested (unlike EIA-positive units) before being released.

Although the virus has been found in many body fluids including blood (35), semen (35,36), saliva (although rarely) (37,38), urine (25), CSF (25,28), tears (39), and breast milk (40), it does not seem to be spread by casual contact. Direct parenteral or mucous membrane exposure to the body fluid of an infected patient is the most likely potential route of transmission to a health care worker. There is but a single case report, from England, which documents an unambiguous seroconversion after such parenteral exposure, in this case a needlestick injury with a contaminated needle (41).

In the United States medical literature, five separate studies involving 666 health care workers receiving direct parenteral or mucous membrane exposure to patients with AIDS or HTLV-III infection have been reported (42). In one study of 44 health care workers parenterally exposed to blood from AIDS patients,

three with no known risk factors were found to be seropositive when first tested. Whether their seroconversion was caused by exposure in the workplace remains uncertain; there were no baseline data and in two of the three cases heterosexual transmission was a possibility (43). In none of the other studies were any patients found to be seropositive in the absence of AIDS risk factors. Exposure of mucous membranes to potentially contaminated body fluids has not resulted in any reported cases of seroconversion.

The anesthesiologist is faced with the following situation. He or she is exposed daily to the body fluids of many patients, a few of whom, perhaps 0.5%, are infected with the HTLV-III virus. Most of these people are asymptomatic carriers, not clearly identifiable. While caring for the general population at low risk for AIDS, the likelihood that the anesthesiologist will become infected with the virus appears to be very small. Seroconversion, even after parenteral exposure to the body fluids of a patient with fullblown AIDS, is uncommon. But what if one does seroconvert after an exposure? Even if one does not develop AIDS or a related condition, one may become an HTLV-III carrier capable of transmitting the virus to others. The latter is a severe consequence for anyone, and for an anesthesiologist there are serious potential professional repercussions as well, such as possible restrictions in patient care. Although such restrictions have not thus far been instituted, they have been discussed. In the climate of fear that surrounds AIDS, decisions may be made that are based on other than purely medical grounds.

On November 15, 1985, the Centers for Disease Control (CDC) issued guidelines for protecting health care workers, stating that its recommendations should be enforced with all patients (42), not just those known to be infected with HTLV-III. The recommendations that apply most directly to anesthesiologists are summarized below.

Sharp contaminated objects may be infective and should be handled carefully. Needles should not be recapped, bent, broken, removed from disposable syringes, or otherwise manipulated by hand before being discarded into puncture-resistant containers. Such containers should be kept as near as possible to the areas where sharp disposable objects are used. Avoid exposure to blood and other body fluids. Gloves alone may be sufficient when handling contaminated objects, but if more extensive contact with body fluids is expected, then gowns, masks, and eye-coverings may be appropriate. Hands that become contaminated should be thoroughly washed as soon as possible. To avoid the need for mouth-to-mouth resuscitation, emergency ventilatory devices such as airways

and bags should be readily available in areas where their use is predictable. Infants delivered from women who become infected with HTLV-III during their pregnancy are at an increased risk of perinatal infection.

Sterilization and disinfection procedures currently in routine use in health care facilities are adequate for instruments and nondisposable items contaminated with blood or body fluids from patients infected with HTLV-III. Items that touch intact mucous membranes should receive "high level disinfection." This includes such anesthesia-related tools and devices as laryngoscope blades, temperature probes, and esophageal stethoscopes. Household bleach, a solution of sodium hypochlorite, is an inexpensive and very effective germicide when diluted from 1:10 to 1:100, depending on the amount of blood, mucus, and so forth present on the surface to be cleaned and disinfected. Potentially infective waste should be placed and transported in clearly labeled impervious plastic bags. Double bagging should be carried out if the outside of the first bag becomes contaminated with body fluids. Additional details concerning germicides and techniques for decontamination and disposal are discussed in the CDC article.

Whereas much emphasis has been given to the protection of the health care worker from an infected patient, the converse is a potential problem as well. The risk to the patient is greatest when there has been significant trauma providing a portal of entry to the virus. The problem is compounded if the blood or other body fluid of an infected health care worker is able to enter this portal. This combination of conditions might be met during an invasive procedure during which the health care worker cuts himself with a scalpel or sticks himself with a needle. To help avoid such an occurrence, the CDC recommends that all health care workers wear gloves for direct contact with mucous membranes or nonintact skin of all patients. Furthermore, those workers with exudative lesions or weeping dermatitis should refrain from all direct patient care and the handling of patient-care equipment until the lesions heal. The CDC recommends that any patient receiving parenteral or mucous membrane exposure to blood or other body fluids of a health care worker be informed of the incident. Recommendations for follow-up and testing after such an exposure of either a patient or a health care worker are discussed in detail. The CDC is expected to issue additional guidelines in the near future intended to minimize the risk of infection with HTLV-III during invasive procedures.

Precautions such as the routine wearing of gloves and the use of eye-protection devices during procedures such as bronchoscopies may seem excessive to

some; each practitioner must determine the degree of precaution he or she wishes to use. Many may choose to take special care only with patients whom they know to be infected with HTLV-III or whom they perceive to be in a high-risk category. But recognizing these patients requires more than merely receiving an impression. During the preoperative assessment, one should consider asking patients whether they have had a test for antibody to HTLV-III or for the "AIDS virus." Most will not take offense at this question if they understand that the virus is increasingly common and found among all groups and classes of society. Many patients may welcome a chance to talk about AIDS because of the common fear of acquiring it through blood transfusions. An admission of HTLV-III seropositivity by a patient should be entered into his hospital record, and those who have a need to know, such as operating room and recovery room personnel, should be specifically informed of it. Ethics demands great discretion on this matter, as discrimination in such areas as hiring, promoting, and receiving of benefits may face persons whose positive HTLV-III test results become publicly known. Medicolegally, the issue is sensitive as well. California, in an effort to enforce confidentiality, imposes a \$10,000 fine and a prison sentence of up to one year for the willful disclosure of the results of another's HTLV-III antibody test (44).

The incidence of AIDS and related disorders will continue to rise sharply for some time yet, perhaps years, as the immune systems of many of those already infected begin to yield to the attack by HTLV-III. Anesthesiologists may expect to encounter such patients more and more frequently during the performance of routine procedures on the seemingly healthy and during indicated procedures (biopsies, catheter placement, intubations) on the sick.

This is a disease for which there is still no cure; prevention, always important, becomes even more important under these circumstances. The danger of these disorders must not, however, be exaggerated. The virus is not highly contagious and simple barrier protection with gloves and other appropriate garb is effective against it. As this disease plays its course, as cures and vaccines are being sought, the informed anesthesiologist, without excessive anxiety, can continue to treat those unfortunate persons thus afflicted.

References

- Curran JW, Morgan WM, Hardy AM, Jaffe HW, Darrow WW, Dowdle WR. The epidemiology of AIDS: current status and future prospects. *Science* 1985;229:1352-7.
- Oleske J, Minnefor A, Cooper R, et al. Immune deficiency syndrome in children. *JAMA* 1983;249:2345-9.
- Annamann AJ. The acquired immunodeficiency syndrome in infants and children. *Ann Intern Med* 1985;103:734-7.
- Scott GB, Fischl MA, Klimas N, et al. Mothers of infants with the acquired immunodeficiency syndrome. *JAMA* 1985;253:363-6.
- Curran JW, Lawrence DN, Jaffe H, et al. Acquired immunodeficiency syndrome (AIDS) associated with transfusions. *N Engl J Med* 1984;310:69-75.
- Feorino PM, Jaffe HW, Palmer E, et al. Transfusion-associated acquired immunodeficiency syndrome: evidence for persistent infection in blood donors. *N Engl J Med* 1985;312:1293-6.
- Harris C, Small CB, Klein RS, et al. Immunodeficiency in female sexual partners of men with the acquired immunodeficiency syndrome. *N Engl J Med* 1983;308:1181-4.
- Redfield RR, Markham PD, Salahuddin SZ, et al. Frequent transmission of HTLV-III among spouses of patients with AIDS-related complex and AIDS. *JAMA* 1985;253:1571-3.
- Redfield RR, Markham PD, Salahuddin SZ, Wright DC, Sarnagadharan MG, Gallo RC. Heterosexually acquired HTLV-III/LAV disease (AIDS-related complex and AIDS): epidemiologic evidence for female-to-male transmission. *JAMA* 1985;254:2094-6.
- Piot P, Taelman H, Minlangu KB, et al. Acquired immunodeficiency syndrome in a heterosexual population in Zaire. *Lancet* 1984;ii:65-9.
- Van de Perre P, Lepage P, Kestelyn P, et al. Acquired immunodeficiency syndrome in Rwanda. *Lancet* 1984;ii:62-5.
- Pape JW, Liautaud B, Thomas F, et al. The acquired immunodeficiency syndrome in Haiti. *Ann Intern Med* 1985;103:674-8.
- Fauci AS, Masur H, Gelmann EP, Markham PD, Hahn BH, Lane HC. The acquired immunodeficiency syndrome: an update. *Ann Intern Med* 1985;102:800-13.
- Landesman SH, Ginzburg HM, Weiss SH. Special report: the AIDS epidemic. *N Engl J Med* 1985;312:521-5.
- Bowen DL, Lane HC, Fauci AS. Immunopathogenesis of the acquired immunodeficiency syndrome. *Ann Intern Med* 1985;103:704-9.
- Lane HC, Fauci AS. Immunologic reconstitution in the acquired immunodeficiency syndrome. *Ann Intern Med* 1985;103:714-8.
- Maloney MJ, Cox F, Wray BB, Guill MF, Hagler J. AIDS in a child 5½ years after a transfusion. *N Engl J Med* 1985;312:1256-7.
- Mølbye M, Biggar RJ, Ebbesen P, et al. Seroepidemiology of HTLV-III antibody in Danish homosexual men: prevalence, transmission, and disease outcome. *Br Med J* 1984;289:573-5.
- Curran JW. The epidemiology and prevention of the acquired immunodeficiency syndrome. *Ann Intern Med* 1985;103:657-62.
- Abrams DI, Lewis BJ, Beckstead JH, Casavant CA, Drew WL. Persistent diffuse lymphadenopathy in homosexual men: endpoint or prodrome? *Ann Intern Med* 1984;100:801-8.
- Mathur-Wagh U, Spigland I, Sacks HS, et al. Longitudinal study of persistent generalized lymphadenopathy in homosexual men: relation to acquired immunodeficiency syndrome. *Lancet* 1984;i:1033-8.
- Gallo RC, Wong-Staal F. A human T-lymphotropic retrovirus (HTLV-III) as the cause of the acquired immunodeficiency syndrome. *Ann Intern Med* 1985;103:679-89.
- Hirsch MS, Kaplan JC. Prospects of therapy for infections with human T-lymphotropic virus type III. *Ann Intern Med* 1985;103:750-5.
- Shaw GM, Harper ME, Hahn BH, et al. HTLV-III infection in brains of children and adults with AIDS encephalopathy. *Science* 1985;227:177-82.
- Levy JA, Kaminsky LS, Morrow WJW, et al. Infection by the retrovirus associated with the acquired immunodeficiency syndrome. *Ann Intern Med* 1985;103:694-9.

26. Resnick L, diMarzo-Veronese F, Schupbach J, et al. Intra-blood-brain-barrier synthesis of HTLV-III-specific IgG in patients with neurologic symptoms associated with AIDS or AIDS-related complex. *N Engl J Med* 1985;313:1498-504.
27. Holland JC, Tross S. The psychosocial and neuropsychiatric sequelae of the acquired immunodeficiency syndrome and related disorders. *Ann Intern Med* 1985;103:760-4.
28. Ho DD, Rota TR, Schooley RT, et al. Isolation of HTLV-III from cerebrospinal fluid and neural tissues of patients with neurologic syndromes related to the acquired immunodeficiency syndrome. *N Engl J Med* 1985;313:1493-7.
29. Goldsmith MF. HTLV-III testing of donor blood imminent; complex issues remain. *JAMA* 1985;253:173-81.
30. Schorr JB, Berkowitz A, Cumming PD, Katz AJ, Sandler SG. Prevalence of HTLV-III antibody in American blood donors. *N Engl J Med* 1985;313:384-5.
31. Sivak SL, Wormser GP. How common is HTLV-III infection in the United States? *N Engl J Med* 1985;313:1352.
32. Petricciani JC. Licensed tests for antibody to human T-lymphotropic virus type III: sensitivity and specificity. *Ann Intern Med* 1985;103:726-9.
33. Lederman MM, Ratnoff OD, Evatt BL, McDougal JS. Acquisition of antibody to lymphadenopathy-associated virus in patients with classic hemophilia (factor VIII deficiency). *Ann Intern Med* 1985;102:753-7.
34. Petricciani JC, McDougal JS, Evatt BL. Case for concluding that heat-treated, licensed anti-haemophilic factor is free from HTLV-III. *Lancet* 1985;ii:890-1.
35. Ho DD, Schooley RT, Rota TR, Kaplan JC, Flynn T. HTLV-III in the semen and blood of a healthy homosexual man. *Science* 1984;226:451-3.
36. Zagury D, Bernard J, Leibowitch J, et al. HTLV-III in cells cultured from semen of two patients with AIDS. *Science* 1984;226:449-51.
37. Groopman JE, Salahuddin SZ, Sarngadharan MG, et al. HTLV-III in saliva of people with AIDS-related complex and healthy homosexual men at risk for AIDS. *Science* 1984;226:447-9.
38. Ho DD, Byington RE, Schooley RT, Flynn T, Rota TR, Hirsch MS. Infrequency of isolation of HTLV-III virus from saliva in AIDS. *N Engl J Med* 1985;313:1606.
39. Fujikawa LS, Salahuddin SZ, Palestine AG, Masur H, Nussenblatt RB, Gallo RC. Isolation of human T-lymphotropic virus type II from the tears of a patient with the acquired immunodeficiency syndrome. *Lancet* 1985;ii:529-30.
40. Thiry L, Sprecher-Goldberger S, Jonckheer T, et al. Isolation of AIDS virus from cell-free breast milk of three healthy virus carriers. *Lancet* 1985;ii:891-2.
41. Anonymous. Needlestick transmission of HTLV-III from a patient infected in Africa. *Lancet* 1984;ii:1376-7.
42. Anonymous. Summary: recommendations for preventing transmission of infection with human T-lymphotropic virus type III/lymphadenopathy-associated virus in the workplace. Atlanta, Georgia: Centers for Disease Control; MMWR 1985; 34:681-95.
43. Weiss SH, Saxinger WC, Rechtman D, et al. HTLV-III infection among health care workers: association with needle-stick injuries. *JAMA* 1985;254:2089-93.
44. Silverman MF, Silverman DB. AIDS and the threat to public health. *Hasting Center Report* 1985;(Aug):19-22.

Clinical Reports

Physostigmine Reversal of General Anesthesia for Intraoperative Neurological Testing: Associated EEG Changes

Alan A. Artru, MD, and Geoffrey S. Hui, MS, MD

Physostigmine has been reported to reverse central anticholinergic toxicity (1), drug-induced sedation (2,3), postanesthetic (halothane/nitrous oxide) somnolence (4), respiratory depression (5-7), and delirium (8,9). The use of physostigmine to awaken a patient during anesthesia to allow intraoperative testing of sensory and motor function has not previously been reported. We present a case where physostigmine was used to achieve return of consciousness during general anesthesia to permit intraoperative neurological testing ("wake-up" testing).

An added consideration in this case was that the request for wake-up testing was unexpected. Though all anesthetics were discontinued at the time of the request, 35 min elapsed without the patient awakening. Physostigmine was then administered, and the patient abruptly awakened intraoperatively. While intubated and in the prone position, the patient was able to respond to commands and questions and indicated feeling no discomfort.

The decision to administer physostigmine was aided by the observation that no change in the amplitude or frequency of the electroencephalogram (EEG) toward an "awake" pattern had occurred during the previous 20 min after discontinuance of anesthetics. An abrupt transition of EEG amplitude and frequency to an awake pattern was observed as soon as physostigmine was given.

Case Report

A 23-yr-old, 57-kg woman was scheduled for an elective reduction and lumbar spine fusion with Harrington Rod placement (T₉-L₂) after suffering a burst fracture of the L-1 vertebral body one week earlier in a ski injury. During the week prior to operation she was kept at bedrest in a body jacket. Preoperative roentgenograms revealed 20-30° kyphosis at the thoracolumbar junction. A CT scan showed 20% narrowing of the spinal canal, which was not considered to be critical. She had no neurological deficit. Otherwise her medical history and physical examination were unremarkable. Preoperatively the surgeons felt that neither intraoperative spinal cord monitoring or a wake-up test would be necessary.

The patient was premedicated with morphine sulfate, 5 mg intramuscularly (IM), scopolamine, 0.4 mg IM, and diazepam, 5 mg given orally 90 min prior to induction of anesthesia. On arrival in the operating room the patient was awake and calm. In addition to placing routine patient monitors, bilateral frontoparietal EEG electrodes were placed, and the EEG was monitored using a Cerebral Function Monitor (CFM) (Model 970, Critikon, Inc., England) (10). Electrodes were adjusted to maintain impedances between electrode pairs at <3 k Ω . The CFM was set so that the value for EEG amplitude, expressed as μ V, was updated each second and represented a running average of the last 14 sec of EEG activity. The value for EEG frequency, expressed as Hz, was updated every 2 sec and also represented a running average of the last 14 sec. Prior to induction of anesthesia, the patient's EEG was characterized by high frequency (10-14 Hz) and low amplitude (10-12 μ V) activity.

Anesthesia was induced with thiopental, 500 mg,

Received from the Department of Anesthesiology, University of Washington School of Medicine, Seattle, Washington. Accepted for publication May 13, 1986.

Address correspondence to Dr. Artru, Department of Anesthesiology RN-10, University of Washington School of Medicine, Seattle, WA 98195.

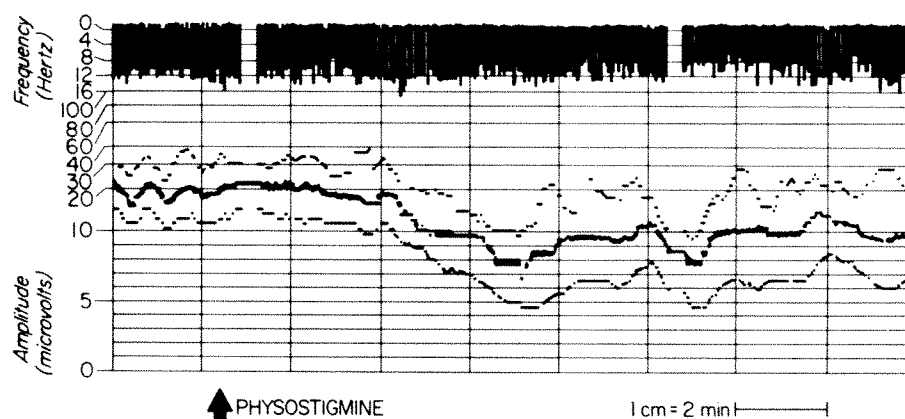


Figure 1. This portion of the CFM tracing shows the effects of administration of physostigmine, 2 mg. The arrow shows where the first 1-mg dose was administered. A second 1-mg dose was administered 2 min later. About 1.5 min after the second dose of physostigmine, the EEG amplitude decreased, EEG frequency increased, and the patient awakened. Frequency (0–16 Hz) is displayed on the upper portion of the tracing, and amplitude (0–100 μ V) is displayed on the lower portion of the tracing. The CFM is set on the "average" mode. In this mode the solid horizontal line represents mean EEG amplitude (see text), and the broken lines represent the range of EEG amplitude. The paper speed is 0.5 cm/min. Gaps in the tracing (top) denote 10-min intervals.

and fentanyl, 200 μ g intravenously (IV). Pancuronium bromide, 5 mg IV, was given for muscle relaxation. Anesthesia was maintained with nitrous oxide (N_2O), 65%, and halothane, 1%, in oxygen with the patient in the prone position. Expired concentrations of anesthetic gases were analyzed by on-line mass spectrometry. During this period of anesthesia, the EEG was characterized by low frequency (6–10 Hz) and high amplitude (22–28 μ V) activity consistent with halothane anesthesia.

Approximately 3 hr after induction, upon reduction of the vertebral column and placement of Harrington rods, the surgeons requested a wake-up neurological test. Accordingly, administration of halothane and N_2O was discontinued. Fifteen minutes later EEG frequency had increased to 10–14 Hz and EEG amplitude decreased to 16–21 μ V, consistent with partial reversal of anesthesia. However, the patient did not awaken. Thirty-five minutes after all anesthetic gases were turned off and the mass spectrometer detected negligible amounts of N_2O and halothane in the breathing circuit, the patient was still unresponsive to command and pain. Train-of-four stimulation showed no twitch depression, indicating that lack of patient responsiveness was not due to impaired neuromuscular function. No change of EEG frequency or amplitude occurred during the final 20 min of this 35-min period.

In an effort to effect complete reversal of anesthesia, physostigmine, 1 mg IV was given, followed by a second 1-mg dose 2 min later. A transient decrease in heart rate to 60 from 90 beats/min was noted, but no treatment was necessary. Approximately 1.5 min after the second dose of physostigmine the patient abruptly awoke from anesthesia and became responsive to verbal commands. Transition to the awakened state was accompanied by a return of EEG activity

to a high frequency (10–16 Hz) and low amplitude (8–12 μ V) pattern similar to that observed prior to induction of anesthesia (Fig. 1). Neurological testing clearly demonstrated new sensory and motor deficits in both legs. The patient remained awake for approximately 60 min, during which time repeated sensory and motor testing of the lower extremities was performed as the position of the Harrington rods was altered. The patient was fully cooperative to repetitive testings, yet signaled when questioned that she was not uncomfortable and displayed no signs of stress (e.g., tachycardia, sweating). Fentanyl, 75 μ g IV, was given, and N_2O (65%) in oxygen was administered intermittently during the last 30 min of the 60 min of neurological testing. The patient was verbally and tactually assured at all times.

Eventually all hardware had to be removed before some motor function returned to the left leg. For closure of the wound the patient was reanesthetized with diazepam, 10 mg IV, and N_2O (60%) and halothane (1%) in oxygen. Anesthesia was associated with a return to low frequency (9–12 Hz), high amplitude (25–32 μ V) EEG activity. The remainder of the anesthetic was uneventful. When interviewed postoperatively, the patient had no recall of having been awakened during surgery. Two months later she was discharged with residual weakness in the right ankle only.

Discussion

In the present case, the patient received morphine, scopolamine, and diazepam for preoperative sedation; thiopental and fentanyl for induction; and N_2O and halothane for maintenance of anesthesia. It is not certain which drug(s) caused the patient's obtundation during the first 35 min of the attempted wake-

up test, or which was/were reversed by physostigmine to cause awakening. Physostigmine, for example, reverses the sedation and delirium caused by scopolamine (11-13), and reverses the sedation (2,5) and respiratory depression (5-7) but not the analgesia (2) produced by morphine. On the other hand, physostigmine may or may not reverse diazepam-induced sedation (3,8,14,15) and had no effect on the level of consciousness of patients in barbiturate coma (16).

Physostigmine appears to reverse drug-induced sedation by increasing central cholinergic activity (17). For drugs that cause sedation by central cholinergic inhibition (e.g., scopolamine), physostigmine reverses the cholinergic depletion, allowing the patient to awaken. For drugs that cause sedation via non-cholinergic pathways (e.g., by accumulation of γ -amino butyrate or stimulation of benzodiazepine receptors) (18), central cholinergic activation may produce arousal by a general analeptic effect.

In addition to reversing sedation, physostigmine may possess an analgesic effect of its own (19-21), and may or may not cause amnesia (22-25). Physostigmine has not been reported to cause the adverse effects that have been noted with naloxone, e.g., reversal of the analgesic effect of narcotics, hypertension, cardiac arrhythmias, and pulmonary edema (26,27).

The EEG changes associated with physostigmine-induced awakening have not been reported previously in humans. However, in a preliminary study in halothane-anesthetized dogs, physostigmine, 0.03 mg/kg IV, shifted EEG activity from a low frequency, high amplitude pattern characteristic of halothane anesthesia to a high frequency, low amplitude awake pattern (28). This shift of EEG activity caused by physostigmine in anesthetized dogs is similar to that caused by physostigmine in the present case.

In this case, monitoring the EEG using the CFM aided the decision to administer physostigmine, as no change in the amplitude or frequency of the EEG toward an awake pattern was observed during the final 20 min of the period of discontinuance of anesthetics. The "awake" state that occurred immediately after administration of physostigmine was characterized by EEG activity similar to that recorded prior to induction of anesthesia. In addition, EEG monitoring helped to confirm the success of our attempt to reanesthetize the patient after the wake-up test. When diazepam, N₂O, and halothane were given to reanesthetize the patient 60 min after administration of physostigmine, the patient rapidly became somnolent. The EEG pattern at that time confirmed that an anesthetic state had been achieved because the amplitude and frequency of the EEG were similar to

those observed during anesthesia prior to administration of physostigmine.

In summary, we present a case where physostigmine was used to wake a patient from anesthesia for intraoperative neurological testing. The patient woke abruptly, yet analgesia was preserved and the patient had no recall. When neurological testing was completed, the patient was reanesthetized without difficulty. EEG monitoring was useful because it aided the decision to administer physostigmine and helped to confirm that an anesthetic state was achieved when anesthetics were administered to the patient 60 min after physostigmine was given.

References

1. Rumack B. Anticholinergic poisoning: treatment with physostigmine. *Pediatrics* 1973;52:449-51.
2. Weinstock M, Davidson JT, Rosin AJ, et al. Effect of physostigmine on morphine-induced postoperative pain and somnolence. *Br J Anaesth* 1982;54:429-33.
3. Bidwai AV, Stanley TH, Rogers C, Riet EK. Reversal of diazepam-induced postanesthetic somnolence with physostigmine. *Anesthesiology* 1979;51:256-9.
4. Hill GE, Stanley TH, Seutker CR. Physostigmine reversal of postoperative somnolence. *Can Anaesth Soc J* 1977;24:707-11.
5. Bourke DL, Rosenberg M, Allen PD. Physostigmine: effectiveness as an antagonist of respiratory depression and psychomotor effects caused by morphine or diazepam. *Anesthesiology* 1984;61:523-8.
6. Smith M, Ketcham TR, Nahrwold ML. Morphine, physostigmine, and respiratory depression. *Anesthesiology* 1981;55:A374.
7. Snir-Mor I, Weinstock M, Davidson JT, Bahar M. Physostigmine antagonizes morphine induced respiratory depression in human subjects. *Anesthesiology* 1983;59:6-9.
8. Larson GF, Hurlbert BJ, Wingard DW. Physostigmine reversal of diazepam-induced depression. *Anesth Analg* 1977;56:348-51.
9. Blitt CD, Petty WC. Reversal of lorazepam delirium by physostigmine. *Anesth Analg* 1975;54:607-8.
10. Schwartz MS, Colvin MP, Prior PF, et al. The cerebral function monitor. Its value in predicting the neurological outcome in patients undergoing cardiopulmonary bypass. *Anaesthesia* 1973;28:611-8.
11. Duvoisin R, Katz R. Reversal of central anticholinergic syndrome in man by physostigmine. *JAMA* 1968;206:1963-5.
12. Cromwell EB Jr, Ketchum JS. The treatment of scopolamine induced delirium with physostigmine. *Clin Pharmacol Ther* 1967;8:409-17.
13. Holzgrafe RE, Vondrell JJ, Mintz SM. Reversal of postoperative reactions to scopolamine with physostigmine. *Anesth Analg* 1973;52:921-5.
14. Garber JG, Ominsky AJ, Orkin FK, et al. Physostigmine-atropine fails to reverse diazepam sedation. *Anesth Analg* 1980;59:58-60.
15. Spaulding BC, Choi SD, Gross JB, et al. The effect of physostigmine on diazepam-induced ventilatory depression: a double blind study. *Anesthesiology* 1984;61:551-4.
16. Nilsson E, Meretoja OA, Pertti N. Hemodynamic responses to physostigmine in patients with a drug overdose. *Anesth Analg* 1983;62:885-8.
17. Beani L, Bianchi C, Santinoceto L, et al. The cerebral acetyl-

- choline release in conscious rabbits with semi-permanently implanted epidural cups. *Int J Neuropharmacol* 1968;7:469-81.
18. Costa E, Guidotti A, Mao CC, et al. New concepts on the mechanism of action of benzodiazepines. *Life Sci* 1975;17:167-86.
 19. Pellandra CL. La génésérine-morphine adjuvant de l'anesthésia générale. *Lyon Med* 1933;151:653-62.
 20. Floodmark S, Wramner T. The analgesic action of morphine eserine and prostigmine studied by a modified Hardy-Wolff-Goodell method. *Acta Physiol Scand* 1945;9:88-96.
 21. Sitaram N, Buchsbaum MS, Gillin JC. Physostigmine analgesia and somatosensory evoked responses in man. *Eur J Pharmacol* 1977;42:285-90.
 22. Pandit UA, Kothary SP, Samra SK, et al. Physostigmine fails to reverse clinical, psychomotor or EEG effects of lorazepam. *Anesth Analg* 1983;62:679-85.
 23. Davis KL, Hollister LE, Overall J, et al. Physostigmine: effects on cognition and affect in normal subjects. *Psychopharmacology* 1976;51:23-7.
 24. Ghoneim MM, Mewaldt SP. Studies on human memory. The interactions of diazepam, scopolamine, and physostigmine. *Psychopharmacology* 1977;52:1-6.
 25. Davis KL, Mohs RC, Tinklenberg JR, et al. Physostigmine: improvement of long-term memory processes in normal humans. *Science* 1978;201:272-4.
 26. Azar I, Turndorf H. Severe hypertension and multiple atrial premature contractions following naloxone administration. *Anesth Analg* 1979;58:524-5.
 27. Prough DS, Roy R, Bumgarner J, et al. Acute pulmonary edema in healthy teenagers following conservative doses of intravenous naloxone. *Anesthesiology* 1984;60:485-6.
 28. Roy RC, Stulken EH Jr. EEG arousal by doxapram, naloxone, and physostigmine. *Anesthesiology* 1979;51:S47.

Posterior Dislocation of the Shoulder Complicating Regional Anesthesia

Donald Pagden, MBBS, Anni S. Halaburt, MD, Romuald Wirpszo, MD, and Andrzej Karyn, MD

The connection between convulsive seizures and skeletal injuries is well-known. These injuries result from the violent forces generated by the abrupt and synchronous contractions of powerful muscle groups. We present an account of two cases of posterior dislocation of the shoulder caused by convulsions after regional anesthesia. There is no previous report of this complication in the English language literature.

Case 1

A previously healthy 64-yr-old woman weighing 59 kg was scheduled for surgery for uterine prolapse. Her physical status was normal, as were the results of routine laboratory tests and an ECG. One hour after premedication, an intravenous infusion of Ringer's solution was started. After skin preparation and draping, a short-bevel 18-gauge needle was inserted into the sacral canal and advanced for about 4 cm. Aspiration with repeated rotation of the needle was negative. Injection of 2 ml of 0.5% bupivacaine with epinephrine met with no resistance. After a pause, when no untoward reaction became apparent, a further 18 ml was injected in small increments with a pause between each for further aspiration attempts. As the needle was withdrawn, the patient abruptly developed generalized clonic convulsions. She was immediately given thiopental, 125 mg, and diazepam, 10 mg, while being ventilated by bag and mask. Within a minute the convulsions subsided and spontaneous breathing resumed. She was now moderately cyanotic and had a rapid pulse and a systolic blood pressure of only 70 mm Hg. With continued oxygenation and the infusion of 500 ml colloid solution, her vital signs became normal within approximately 20 min. After

some hesitation it was decided that surgery would proceed as planned. It became apparent, however, that the intended caudal block had failed, and general anesthesia was therefore induced.

On recovering consciousness, the patient made persistent complaints of pain in both shoulders. After analgesics failed to prove helpful, it was found that both shoulders were swollen and that active and passive movements were extremely restricted and painful. X-ray examination revealed a three-part fracture of the upper end of the left humerus with posterior dislocation of the head (Fig. 1) and posterior dislocation of the right shoulder with a typical compression fracture of the head of the humerus (Fig. 2).

The injury to the right shoulder was treated by manipulative reduction and immobilization; recovery was eventually complete. The left shoulder required open reduction and mechanical fixation of the fragments. Although 10 years have now elapsed since this event, the patient still has a stiff and painful left shoulder with a restricted range of movements.

Case 2

A 51-yr-old man weighing 81 kg was to undergo surgery for a right inguinal hernia repair. Because of mild hypertension he was assigned to ASA category II. Preoperative laboratory tests, chest x-ray and ECG were all normal.

Infusion of a buffered salt-dextrose solution was started 1 hr after premedication, and the patient was then connected to an ECG monitor and turned onto his right side. After skin preparation and draping, an 18-gauge Tuohy needle was inserted into the epidural space at the L2-3 level. Aspiration using a 10-ml glass syringe was negative in all four quadrants. A test dose of 4 ml 5% bupivacaine with epinephrine was injected. Four minutes later, there having been no reaction, three 5-ml increments were given slowly and with a pause for aspiration attempts between each. The needle

Received from the Departments of Anesthesia and Radiology, County General Hospital, Ljungby, Sweden. Accepted for publication April 21, 1986.

Address correspondence to Dr. Pagden, Department of Anaesthesia, Ljungby Lasarett, S-341 00 Ljungby, Sweden.



Figure 1. Three-part fracture of the upper end of the left humerus with dislocation of the shoulder. Note: This film does not reveal the posterior location of the humeral head with respect to the glenoid, for which special views are necessary.

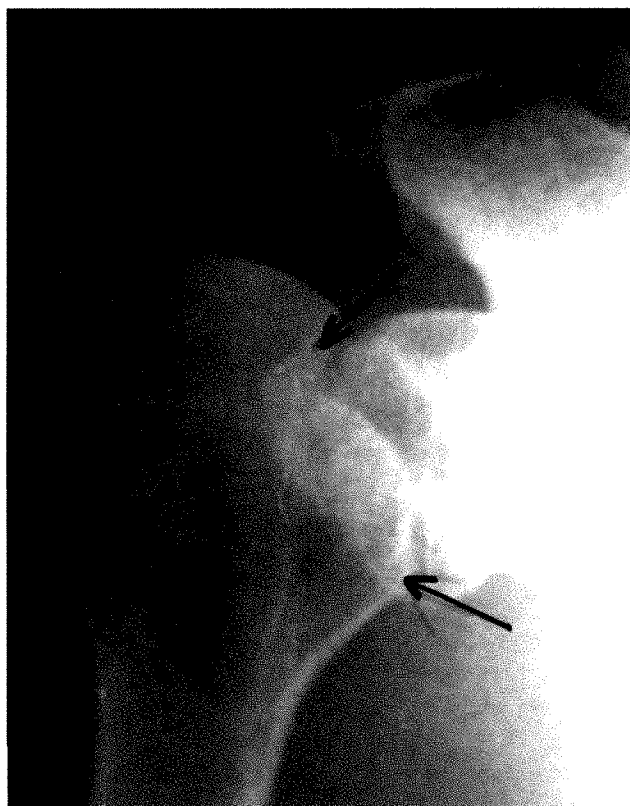


Figure 2. Anteromedial compression fracture of the head of the right humerus (margins indicated by arrows) characteristic of posterior dislocation of the shoulder. Note: This film does not reveal the posterior location of the humeral head with respect to the glenoid, for which special views are necessary.

was then removed, and the patient returned to the supine position, upon which he lost consciousness and developed severe generalized convulsions. He was immediately given succinylcholine, 100 mg, and diazepam, 30 mg, followed by tracheal intubation and ventilation with 100% oxygen. The convulsions subsided almost at once, and spontaneous breathing was soon reestablished. Because his blood pressure had not decreased and his general condition was good, it was decided to go ahead with surgery. Anesthesia was maintained with a 2:1 nitrous oxide-oxygen breathing mixture and two further 10-mg increments of diazepam.

On waking up it was noted that the patient had motor and sensory blockade fully consistent with normal epidural anesthesia. Shortly afterwards, however, he began to complain of pain in his left shoulder. Analgesics provided little relief, and x-ray examination revealed posterior dislocation of the shoulder with a four-part fracture of the upper end of the humerus. Open reduction of the dislocation with mechanical

fixation of the fractures was carried out the following day. During the 2 years that have now passed, progress has been very slow, and it seems unlikely that recovery will be complete.

Discussion

Posterior dislocation of the shoulder is an unusual injury; the average reported incidence is about 2% of all shoulder dislocations (1). The condition is usually caused by convulsions; when bilateral—as it often is—this association is virtually certain (2). These dislocations are frequently accompanied by fractures of the head and neck of the humerus, often of startling severity (3). Other skeletal injuries reported after convulsions include central acetabular fracture-dislocations and fractures of the vertebrae, the pelvis, and the neck of the femur (3,4,5,6).

The most frequently reported cause of these injuries is epileptic or epileptiform convulsions, including those induced electrically or pharmacologically for

therapeutic purposes (1,6). Other causes include hyponatremia (4,5), eclampsia (7), accidental electrocution (8), and hypocalcemia after parathyroidectomy (9). To quote Lovelock and Monaco (4), "It is likely that any cause of convulsions may result in a similar type of injury."

Because it is generally agreed that convulsions are seen in 1-2 patients per thousand after regional anesthesia, it was perhaps inevitable that skeletal injuries would sooner or later be reported in this context. The disturbing events recorded in our two case reports undermine any complacency about such convulsions. To view such episodes as intrinsically harmless warning signs of possibly impending cardiovascular failure is unwarranted, and the concept of a "margin of safety" between convulsions and cardiovascular collapse (10,11) may be a dangerous delusion. The same must be said of the assertion that toxic reactions to local anesthetic agents need not give rise to sequelae if promptly and adequately treated (12).

In summary, convulsions after regional anesthesia—despite prompt and adequate treatment—are no less likely to result in skeletal injuries than other convulsive episodes regardless of cause. This should be taken into account in any assessment of the overall safety of regional anesthesia.

References

1. Nobel W. Posterior traumatic dislocation of the shoulder. *J Bone Joint Surg* 1962;44A:523.
2. Din KM, Meggit BF. Bilateral four-part fractures with posterior dislocation of the shoulder. *J Bone Joint Surg* 1983;65B:176.
3. Shaw JL. Bilateral posterior fracture-dislocation of the shoulder and other trauma caused by convulsive seizures. *J Bone Joint Surg* 1971;53A:1437.
4. Lovelock JE, Monaco LP. Central acetabular fracture dislocations: An unusual complication of seizures. *Skeletal Radiol* 1983;10:91-4.
5. Remec PT, Evarts CMcC. Bilateral central dislocation of the hip. *Clin Orthop Rel Res* 1983;181:118-20.
6. Powell HDW. Simultaneous bilateral fractures of the neck of the femur. *J Bone Joint Surg* 1960;42B:236.
7. Varma AN, Seth SK, Verma M. Simultaneous bilateral central dislocation of the hip—an unusual complication of eclampsia. *J Trauma* 1981;21:499-500.
8. O'Flanagan PH. Fracture due to shock from domestic electricity supply. *Injury* 1975;6:244.
9. Davies DR, Friedman M. Complications after parathyroidectomy. *J Bone Joint Surg (Br)* 1966;48:117.
10. Marx GF. Cardiotoxicity of local anesthetics: The plot thickens. *Anesthesiology* 1984;60:3-5.
11. Mallampati SR, Liu PL, Knapp RM. Convulsions and ventricular tachycardia from bupivacaine with epinephrine: Successful resuscitation. *Anesth Analg* 1984;63:856-9.
12. Moore DC, Bonica JJ. Convulsions and Ventricular Tachycardia from Bupivacaine with Epinephrine: Successful Resuscitation—Congratulations! (Letter). *Anesth Analg* 1985;64:843-8.

A Serious Complication due to Gastrointestinal Malfunction in a Patient with Myotonic Dystrophy

Yumiko Ishizawa, MD, Hiroshi Yamaguchi, MD, Shuji Dohi, MD, and Kanji Koyama, MD

Myotonic dystrophy is an inherited autosomal dominant multisystem disease involving the neuromuscular (1-5), respiratory (1,2,6-11), and cardiovascular systems (1,2,10,11). Resulting problems, such as decreased ventilatory capacity, depressed laryngeal reflex, and prolonged muscle contraction with depolarizing muscle relaxant may become potential hazards during and after anesthesia (3,4,5,10,11). However, although there is a description by Nowak et al. (12) that patients with myotonic dystrophy have poor gastrointestinal motility, little attention has been given to gastrointestinal problems. We describe a patient with myotonic dystrophy who, although his anesthetic course was uneventful, developed aspiration pneumonia, probably due to abnormal gastrointestinal motility after reconstructive surgery for an open bite.

Case Report

A 36-yr-old man (60 kg) was admitted for surgical correction of his anterior open bite. The diagnosis of myotonic dystrophy had been made when he was 18. He had two episodes of aspiration pneumonia in the last decade. On admission, he was found to have typical myopathic facies and distal weakness of limbs, together with the classical sustained grip upon handshake. Along with nasal voice and lingual atrophy, he reported stasis of saliva, but denied any difficulties in swallowing. He denied constipation or diarrhea. Preoperative pulmonary function studies revealed severely decreased vital capacity (42% of the predicted value). A preoperative arterial blood sample while breathing on room air showed a pH of 7.36, a PaO_2 of 69 mm Hg, and a PaCO_2 of 47 mm Hg. His electrocardiogram showed complete right bundle branch block.

Prior to operation, the patient was premedicated with scopolamine, 0.4 mg intramuscularly (IM), and brought to a warmed operating room. With supplementation of diazepam, 3 mg, and fentanyl, 0.1 mg intravenously (IV), his trachea was intubated nasally without the use of muscle relaxants following which anesthesia was induced with fentanyl, 0.1 mg IV, and nitrous oxide (67%). During the operation, anesthesia was maintained with nitrous oxide, 67%, and oxygen, and was supplemented by diazepam (total 10 mg) and fentanyl (0.6 mg). Pancuronium bromide, 3 mg IV, was given because the patient moved his tongue during the operation. The anesthetic course was otherwise uneventful. The operation, which lasted about 3 hr, included maxillomandibular fixation. After the procedure, the patient was alert and able to make weak respiratory efforts. He was transferred to the ICU and mechanically ventilated with the tracheal tube still in place.

On the second postoperative day, the patient's trachea was extubated because he had a tidal volume of 300-350 ml and an expiratory minute volume of 7.2 L. Thereafter his respiratory and circulatory condition remained stable. At the time of extubation the volume of drainage from the nasogastric tube was as much as 600-820 ml/day. Because gastric drainage became bloody, intravenous infusion of 16 mg/hr of cimetidine was instituted for 12 hr/day.

On the fourth postoperative day, normal bowel sounds were heard, and an elemental diet through a nasogastric tube was initiated, even though the amounts of gastric drainage were still large (500 ml/day). A few hours later, he vomited twice. The vomitus was soon removed from his mouth by suction, and the maxillomandibular fixation was released. However, he developed progressive dyspnea and cyanosis. Arterial blood gas tension while breathing room air were PaO_2 48 mm Hg and PaCO_2 49 mm Hg. A chest radiograph showed aspiration pneumonia involving the entire right lung. His trachea was immediately reintubated, several broncheal lavages were done with physiologic saline, and PEEP (5-8 cm H_2O) was added to the mechanical ventilator. After the ep-

Received from the Department of Anesthesiology, University of Tsukuba Hospital, and the Institute of Clinical Medicine, University of Tsukuba, Ibaraki, Japan. Accepted for publication May 16, 1986.

Address correspondence to Dr. Dohi, Institute of Clinical Medicine, University of Tsukuba, Sakura-mura, Ibaraki 305 Japan.

isode of vomiting and aspiration, his bowel sounds were markedly diminished. We decided to leave his trachea intubated until he had normal bowel movements to avoid the risk of repeated aspiration, as the amount of gastric drainage was still large.

For the next few days his bowel sounds gradually became audible, and the volume of gastric drainage decreased to 200–420 ml/day with intravenous infusion of 0.5 mg/hr of prostaglandin F_{2-α} for 8 hr/day. His respiratory condition also had improved. His trachea was extubated 10 days after the reintubation without subsequent difficulties in respiration or swallowing.

Discussion

It has been emphasized in several reports that myotonic dystrophy involves special anesthetic considerations throughout the perioperative period in terms of neuromuscular (1,3–5), respiratory (1,10,11), and cardiovascular function (1,11). However, little attention has been paid to gastrointestinal malfunction in patients with this disease. Although we successfully managed this patient during anesthesia, he vomited and aspirated postoperatively. The vomiting with subsequent aspiration pneumonitis was related to several factors, including impaired gastrointestinal peristalsis (12,13), inadequate closing of the vocal cords (1,2,6,11–15), and the intraoperative need for maxillomandibular fixation. Anesthetics, including narcotics (16) and pancuronium (17), can further depress intestinal peristalsis already diminished by the underlying disease itself and thus can delay gastric emptying.

Patients with myotonic dystrophy commonly have reduced peristalsis in the small intestine, and 35% of such patients complain of diarrhea and abdominal cramping (2,12–15). Furthermore, patients with this disease often have maldevelopment of the maxilla and mandible, requiring surgical correction that includes maxillomandibular fixation for some time in the postoperative period (18). This fixation probably contributed to the aspiration of vomitus that occurred in this case. Because this fixation cannot rapidly be released before aspiration can occur when a patient vomits, maxillomandibular fixation should be avoided after the procedure unless it is surgically absolutely necessary. Kaufman and Friedman (19) have successfully performed this surgical procedure without fixation.

Aspiration of gastric contents is well-known to cause serious pulmonary insufficiency with a high mortality, 55–70% (20). Our successful management of aspiration pneumonitis in the present case may have been based in part on the high pH of gastric juice

resulting from the postoperative administration of cimetidine and use of an elemental diet (pH 6.3–7.3). Prostaglandin F_{2-α} (21), which we used to facilitate return of intestinal peristalsis, may have helped to avoid repeated aspiration.

The present case emphasizes the potential danger of postoperative vomiting and the importance of preventing aspiration due to vomiting in patients with myotonic dystrophy. Emptying of gastric contents and normal gastrointestinal motility must be assured before patients with myotonic dystrophy are extubated postoperatively if such a complication is to be avoided.

The authors thank Dr. H. Naito, Professor and Chairman, Department of Anesthesiology, for his review of the manuscript and Dr. H. Fukuda, Assistant Professor, Department of Dental and Oral Surgery, Institute of Clinical Medicine, University of Tsukuba, for his comments.

References

1. Aldridge LM. Anaesthetic problems in myotonic dystrophy. *Br J Anaesth* 1985;57:1190–30.
2. Harper PS. Smooth Muscle in Myotonic Dystrophy. In: Harper PS, ed. *Myotonic Dystrophy*. Philadelphia: WB Saunders Company, 1979:79–89.
3. Azar I. The Response of patients with Neuromuscular disorders to muscle relaxants: a review. *Anesthesiology* 1984; 61:173–87.
4. Buzello W, Krieg N, Schlickewei A. Hazards of neostigmine in patients with neuromuscular disorders. *Br J Anaesth* 1982; 54:529–31.
5. Boheimer N, Harris JW, Ward S. Neuromuscular blockade in dystrophia myotonica with atracurium besylate. *Anaesthesia* 1985;40:872–4.
6. Pruzanski W, Profis A. Pulmonary disease in myotonic dystrophy. *Am Rev Resp Dis* 1965;91:874–9.
7. Carrol JE, Zwillich CL, Weil JV. Ventilatory response in myotonic dystrophy. *Neurology* 1977;27:1125–8.
8. Begin R, Bureau MA, Lupien L, Lemieux B. Control and modulation of respiration in Steinert's myotonic dystrophy. *Am Rev Resp Dis* 1980;121:281–9.
9. Begin R, Bureau MA, Lupien L, Bernier JP, Lemieux E. Pathogenesis of respiratory insufficiency in myotonic dystrophy. *Am Rev Resp Dis* 1982;125:312–8.
10. Ravin M, Newmark Z, Saviello G. Myotonia dystrophica—an anesthetic hazard. *Anesth Analg* 1975;54:216–8.
11. Mudge BJ, Taylor PB, Vanderspek AFL. Perioperative hazards in myotonic dystrophy. *Anaesthesia* 1980;35:492–5.
12. Nowak TV, Anuras S, Brown BP, Ionasescu V, Green JB. Small intestinal motility in myotonic dystrophy patients. *Gastroenterology* 1984;86:808–13.
13. Harvey JC, Sherbourne DH, Siegel CI. Smooth muscle involvement in myotonic dystrophy. *Am J Med* 1965;39:81–90.
14. Goldberg HE, Sheft DJ. Esophageal and colon changes in myotonia dystrophica. *Gastroenterology* 1972;63:134–9.
15. Simpson AF, Khilnani MT. Gastrointestinal manifestations of

- the muscular dystrophies. *Am J Roentgenol Radium Ther Nucl Med* 1975;125:948-55.
16. Nimmo WS, Wilson J. Narcotic analgesics and delayed gastric emptying during labour. *Lancet* 1975;ii:890-3.
 17. Son SL, Waud DR. A vagolytic action of neuromuscular blocking agents at the pacemaker of the isolated guinea pig atrium. *Anesthesiology* 1978;48:181-4.
 18. Wald C, Bronx. Myotonic dystrophy—sedative and anesthetic management. *Oral Surg* 1975;39:886-92.
 19. Kaufman J, Friedman JM. Myotonic dystrophy: surgical and anesthetic considerations during orthognathic surgery. *J Oral Maxillofac Surg* 1983;41:667-71.
 20. Epstein PE. Aspiration diseases of the lungs. In: Fishman AP, ed. *Pulmonary Diseases and Disorders*. New York: McGraw-Hill Book Company, 2:1327-39.
 21. Wilson DE. Prostaglandins. Their action on the gastrointestinal tract. *Arch Intern Med* 1974;133:112-8.

Lumbar Epidural Anesthesia for Operative and Postoperative Pain Relief in Infants and Young Children

Bernard Dalens, MD, Alain Tanguy, MD, and Jean-Pierre Haberer, MD

General anesthesia is the standard for surgical procedures in infants and young children. Caudal anesthesia is a suitable alternative for urologic and lower abdominal surgery (1,2,3). Orthopedic procedures on the lower limbs would also benefit from epidural anesthesia, but the caudal route might prove hazardous in pediatric patients because of the amounts of local anesthetics necessary to ensure satisfactory motor and sensory blockade. As in adults, lumbar epidural would be more appropriate, but most equipment for epidural anesthesia cannot be used in small children.

In the belief that epidural anesthesia in selected pediatric cases might prove useful 1) in reducing the level of general anesthesia and subsequently the loss of the airway, especially in children with severe respiratory disease, and 2) in improving the postoperative management of pain relief, we selected smaller equipment, including a 20-gauge 3/64 Potts-Cournand^R needle, and undertook a prospective study of lumbar epidural analgesia in young children undergoing orthopedic procedures on the pelvis or the lower extremities and in some cases both the pelvis and lower extremities. On the basis of previous reports (4,5,6), we compared the sensory and motor blocks produced by a mixture of lidocaine and bupivacaine with those produced by a mixture of etidocaine and bupivacaine. We also evaluated the postoperative pain relief produced by these mixtures alone and with the addition of morphine (7,8).

Patients and Methods

Thirty-six infants and children scheduled for orthopedic operations on the pelvis and/or lower extremities were selected for this study (Fig. 1). Informed consent was obtained from their parents. The

patients ranged in age from 2 days to 7 yr and in weight from 2.7 to 19.5 kg, and included 19 boys and 17 girls. Thirty-eight children were healthy (ASA I), three had neurological disorders (ASA II) and the remaining 11 had both neurological and respiratory disorders (ASA III, including a child with Pierre Robin syndrome and congenital heart disease). A total of 52 epidural analgesias were administered to the 36 children.

A preoperative examination made certain there were no dystrophic or infectious lesions of the skin in the area of the L3-S1 interspaces. Scoliosis was not considered an absolute contraindication: two children had this deformity and were included in the series after radiological evaluation of their spines.

All epidural anesthetics were performed under general anesthesia, which was maintained throughout the surgical procedure in 37 cases. Atropine sulfate, 0.02 mg/kg, and diazepam, 0.2 mg/kg, were given for premedication. Inhalation induction with nitrous oxide in 50% oxygen and increasing concentrations of halothane (up to 1.5%) was used in 42 procedures. In ten cases, the children preferred intravenous anesthesia and were given ketamine, 3 mg/kg, for induction.

The epidural set (Fig. 2) consisted of a short-bevel 20-gauge 3/64 Potts-Cournand^R needle, an introducer needle, and a smooth-ended obturator (Becton-DickinsonTM). Epidural penetration was attempted at the L4-5 interspace with the child placed in the lateral decubitus position. The introducer was removed after being passed through the skin and interspinous ligament and replaced by an air-filled plastic syringe with minimum resistance (marketed by PortexTM, England, under the name of "Epidural loss of resistance device"). The Potts-Cournand^R needle was then carefully inserted until the change of resistance was experienced as it penetrated the epidural space. At this stage, the minimum resistance syringe was removed and immediately replaced by the smooth-ended obturator to prevent delayed dural penetration while the anesthetist was preparing to administer the selected anesthetic mixture.

Received from the Department of Anesthesiology and Department of Pediatric Surgery, Hôtel-Dieu, Clermont-Ferrand, France. Accepted for publication May 8, 1986.

Address correspondence to Dr. Dalens, Pavillon Gosselin, Hôtel-Dieu, B.P. 69, 63003 Clermont-Ferrand, France.

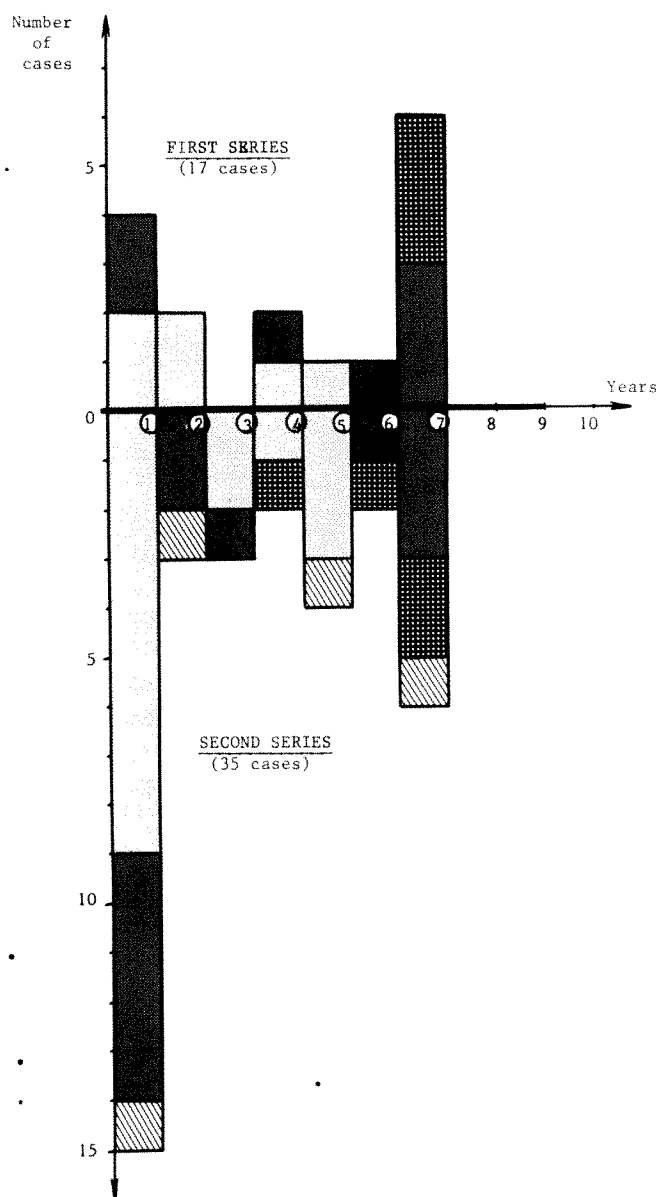


Figure 1. Surgical procedures and patient demographics: club foot, multiple osteotomies and tenotomies, removal of surgical implants and dressings, femoral percutaneous wiring.

An initial series of 17 procedures were performed with the administration of a mixture of 0.5 mg/kg 1% lidocaine and 0.5 mg/kg 0.5% bupivacaine, both with 1:200,000 epinephrine (Table 1). Preservative-free morphine, 0.05 mg/kg, was added to the mixture in 14 cases for postoperative analgesia.

A second series of 35 epidural analgesias were then carried out using a mixture of 0.5 mg/kg 0.5% bupivacaine (with 1:200,000 epinephrine) and 0.5 mg/kg 1% etidocaine without epinephrine (Table 2). A 0.05

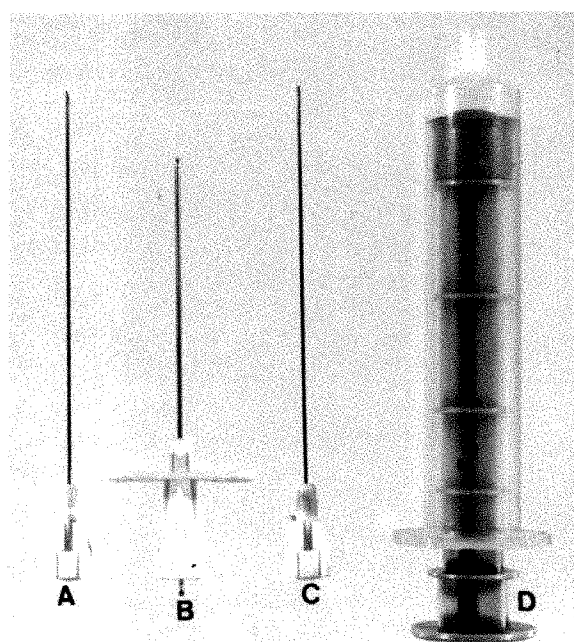


Figure 2. Epidural set. A, introducer needle; B, Potts-Cournand[®] needle; C, Smooth-ended obturator; D, Minimum resistance syringe ("Epidural loss of resistance device" from Portex[™]).

mg/kg dose of morphine was added to this mixture in 27 cases.

After the anesthetic had been injected, the needle was removed and the child was placed in the supine position for at least 15 min before the operation proceeded; all surgical procedures were performed with the child still in this position. Except in one case (Pierre Robin syndrome with congenital heart disease), the children were not intubated and spontaneous breathing was maintained in all cases.

Light general anesthesia was maintained during 37 of the 52 operations, by means of inhalation agents (nitrous oxide in 50% oxygen and 0.25–0.5% halothane) in 34 cases, and intravenous ketamine, 1 mg/kg, in three cases.

We monitored the electrocardiographic and respiratory tracings continuously, and the blood pressure every 3 min (Dinamap[®]) during the procedure and for the 5 hr after the epidural administration of anesthetic agents. Sensory blockade was considered complete when no intravenous analgesics were necessary to achieve the surgical procedure. The level of anesthesia was estimated at the end of the operation by pain stimulus. The duration of anesthesia was evaluated as the time elapsed from epidural penetration to the first spontaneous cries or complaints.

The results were expressed as means \pm SD. Com-

Table 1. Anesthetic Management and Side-Effects in the First Series (Lidocaine and Bupivacaine \pm Morphine)

Events	Club foot	Osteotomies and tenotomies	Removal of implants and dressings
Total cases	6	8	3
ASA 2	1	0	1
ASA 3	0	3	0
Epidural morphine added	6	6	0
Awake during surgery	2	3	3
Motor blockade			
Complete	0	0	2
Partial	5	8	0
None	1	0	1
Adverse effects			
Itching	4	7	2
Nausea, vomiting	2	4	0
Urinary retention	4	5	0

parisons were made using both Student's *t*-test and Mann-Whitney's test, and were considered statistically significant when $P < 0.05$.

Results

Placement of the needle in the epidural space was successful in every case, on the first attempt in 46 procedures, on the second attempt in two. Dural penetration occurred in four cases, which included two children with severe deformity of the spine (arthrogryposis multiplex congenita and 90° scoliosis). Replacement of the needle at the L3-4 interspace was successful in all four cases.

The systolic blood pressure did not decrease more than 10 mm Hg and the heart rate did not increase more than 10 beats/min in 51 of the 52 procedures. A 6.5-year-old child with severe mental retardation was the only case in which hypotension developed, the blood pressure decreasing from 91/52 mm Hg preoperatively to 69/38 mm Hg 15 min after epidural administration of anesthesia.

The respiratory rate did not vary significantly during the first 5 hr after the epidural anesthesia in both groups, whether the children received morphine or not.

Complete sensory blockade was obtained in every case and no additional intravenous analgesics was necessary. The mean level of anesthesia was T6-T7, with extremes ranging from T4-T11. The motor block was poor or absent in the first series (Table 1), which

Table 2. Anesthetic Management and Side-Effects in the Second Series (Bupivacaine and Etidocaine \pm Morphine)

Events	Club foot	Osteotomies and tenotomies	Removal of implants	Femoral wiring
Total cases	15	12	4	4
ASA 2	2	1	0	0
ASA 3	0	3	1	1
Epidural morphine added	14	12	1	0
Awake during surgery	1	3	2	0
Motor blockade				
Complete	15	12	4	4
Partial or none	0	0	0	0
Adverse effects				
Itching	15	11	3	3
Nausea, vomiting	3	6	1	0
Urinary retention	4	5	1	0

impeded the surgeon's work in eight cases, including six out of the eight children who were awake during the surgical procedure.

In the second series (Table 2), in which patients were given epidural bupivacaine plus etidocaine, complete muscle paralysis of the lower extremities was present and those who were anesthetized during the surgical procedure were considered by the surgeon to have muscle relaxation equal to that produced during general anesthesia with muscle relaxants.

All 28 anesthetized children in the second series and all nine in the first were awake at the end of the surgical procedure without any complication or delay.

Itching (nose and eyelids rubbing) was the most frequent postoperative side-effect in both groups, irrespective of whether the children received epidural morphine or not: it was definitely present in 46 cases and we could not be sure that pruritus did not occur in the six remaining children because of their neurological (immaturity, mental retardation) or orthopedic (severe arthrogryposis) status.

Only children who received morphine experienced other side-effects, namely nausea and vomiting (16 cases) and urinary retention (19 cases), the latter being reversed by naloxone in 18 cases. Myosis and respiratory depression were not observed.

The duration of analgesia in the postoperative period when epidural morphine was given (17 hr 05 min \pm 3 hr 20 min in the first and 20 hr 42 min \pm 5 hr 21 min in the second series) was significantly greater than that observed when epidural morphine was not given (respectively, 3 hr 45 min \pm 35 min and 4 hr 36 min \pm 54 min). Comparisons of the two series

showed significant differences only when morphine was added, but individual variations were high, as seen by the large standard deviations.

Discussion

The Potts-Cournand^R needle was developed for arteriographic procedures, but it has characteristics making it useful for epidural penetration, even in neonates. It is small (20 gauge) and its bevel is short, with a cutting edge that is not very sharp. The introducer needle allows easy skin penetration, and the smooth-ended obturator prevents drug reflux as well as delayed dural puncture caused by motion of the tip of the needle.

The subarachnoid space was accidentally entered four times. This incidence may be considered excessive and may be reduced with experience. However, dural puncture will probably not be completely eliminated in the types of patients we studied because the anatomic deformities in many of the children undergoing corrective orthopedic operations are often extreme.

General anesthesia, which is usual in these age ranges (1), was used in every case to ensure safe epidural puncture. In some cases general anesthesia was discontinued after epidural injection and the children remained conscious during the surgical procedure. This was often not satisfactory from the surgical point of view and we think it better to maintain light anesthesia.

Complete sensory blockade was obtained in every case, but sufficient motor blockade was produced only with the second mixture (bupivacaine plus etidocaine). In their study, Chamberlain and Crawford (9) compared the effects of similar anesthetic mixtures on adults. Some of the effects that we observed in young children were significantly different from those observed in adults: the level of sensory blockade was not higher in the first than in the second series, and motor blockade was poor or absent in the first series. We did not use 0.75% bupivacaine because of the hazard of toxicity, and the etidocaine solution we used was more dilute than that used by Chamberlain and Crawford, although the ratio between the two drugs (1% vs 1.5%) was similar in our study and in theirs.

The addition of morphine to the anesthetic mixture produced enduring postoperative pain relief, as is usually reported (10,11,12,13). Itching, namely nose and eyelids rubbing, was a general feature in children who were administered epidural preservative-free morphine but also in those who were not. This effect was not expected in cases not given morphine and its basis remains unclear, particularly because it did

not appear (in our experience) when similar anesthetic mixtures were administered by the caudal route for other surgical procedures (urologic or lower abdominal surgery). In spite of its several side-effects and its variability in duration, the epidural administration of 0.05 mg/kg morphine dramatically improved the postoperative course of the children, without any severe complications, such as respiratory disorders.

A considerable improvement in the technique of epidural anesthesia in children would be the development of a small catheter that could be introduced into the epidural space through the Potts-Cournand^R needle. In this way, local anesthetics could be given in fractional doses with subsequent reduction in toxicity and level of anesthesia. Also, the management of postoperative pain relief could be made easier by permitting subsequent administration of local anesthetics as needed.

In conclusion, we report a study on thirty-six children aged 2 days to 7 yr undergoing orthopedic procedures on the lower extremities. These children were given a total of 52 lumbar epidural anesthetics performed under general anesthesia using a 20-gauge Potts-Cournand^R needle. Two mixtures of local anesthetics were used: 1% lidocaine plus 0.5% bupivacaine in 17 cases (first series), and 0.5% bupivacaine plus 1% etidocaine in 35 cases (second series). Morphine was added to the mixture in 14 of the 17 patients in the first series and in 27 in the second series. Complete sensory block was obtained in every case, but satisfactory motor block was produced only in the second series. Itching was the most usual postoperative side-effect and it occurred with the same frequency in both groups irrespective of whether they received epidural morphine or not. Only children who received morphine experienced other side-effects: nausea and vomiting (16 cases) and urinary retention (19 cases). In spite of these adverse effects, the administration of morphine dramatically improved the postoperative course, without any severe complications, such as respiratory disorders.

References

1. Singler RC. Pediatric regional anesthesia. In: Gregory GA, ed. *Pediatric anesthesia*. New York: Churchill Livingstone, 1983:481-518.
2. MacGrown RG. Caudal analgesia in children. Five hundred cases for procedures below the diaphragm. *Anaesthesia* 1982;37:805-18.
3. Jensen BH. Caudal block for post-operative pain relief in children after genital operations. A comparison between bupivacaine and morphine. *Acta Anaesthesiol Scand* 1981;25:373-5.

4. Takasaki M, Dohi S, Kawabata Y, Takahashi T. Dosage of lidocaine for caudal anesthesia in infants and children. *Anesthesiology* 1977;47:527-9.
5. Eyres RL, Kidd J, Oppenheimer R, Brown TCK. Local anesthetic plasma levels in children. *Anaesth Intensive Care* 1978;6:243-7.
6. Eyres RL, Bishop W, Oppenheimer R, Brown TCK. Plasma bupivacaine concentrations in children during caudal epidural analgesia. *Anaesth Intensive Care* 1983;11:20-2.
7. Donovan BD. Patient attitudes to post-operative pain relief. *Anaesth Intensive Care* 1983;11:125-9.
8. Anonymous. Editorial. *Br Med J* 1978;2:517-8.
9. Chamberlain DP, Crawford RD. Integrated electromyographic measurement of abdominal motor blockade in epidural anesthesia: a comparison of bupivacaine and etidocaine. *Anesthesiology* 1981;55:A157.
10. Nordberg G. Pharmacokinetic aspects of spinal morphine analgesia. *Acta Anaesthesiol Scand* 1984;28(suppl. 79):S1-S40.
11. Jones SEF, Beasley JM, Macfarlane DWR, Davis JM, Hall-Davies G. Intrathecal morphine for postoperative pain relief in children. *Br J Anaesth* 1984;56:137-40.
12. Meigner M, Souron R, Le Neel JC. Postoperative dorsal epidural analgesia in the child with respiratory disabilities. *Anesthesiology* 1983;59:473-5.
13. Shapiro LA, Jedeikin RJ, Shalev D, Hoffman S. Epidural morphine analgesia in children. *Anesthesiology* 1984;61:210-2.

Cardiovascular Collapse in an Infant after Caudal Anesthesia with a Lidocaine-Epinephrine Solution

Naoki Matsumiya, MD, Shuji Dohi, MD, Hiroshi Takahashi, MD, Yoichi Kondo, MD, and Hiroshi Naito, MD

The use of epinephrine in local anesthetic solutions is commonly accepted as a standard clinical practice in regional anesthesia. It has been suggested that in using such solutions the epinephrine per se counteracts, at least in part, the cardiac depression associated with local anesthetic toxicity (1-3). It has thus been advocated that the addition of epinephrine to the local anesthetic solution should always be considered in order to avoid life-threatening cardiovascular complications (1-3). As far as we know, epinephrine per se has not been observed to produce a fatal adverse reaction during regional anesthesia (4). However, we experienced a case in which acute circulatory collapse developed after the injection of an epinephrine-lidocaine solution for caudal anesthesia in an infant.

Case Report

A 2-month-old, 5.5-kg male infant was scheduled for left inguinal herniorrhaphy. He had no previous medical history. On arrival in the operating room he was crying and his systolic blood pressure and heart rate were 103 mm Hg and 178 beats/min, respectively. Under general anesthesia with halothane (1.5%), nitrous oxide (67%), and oxygen (33%) by mask and receiving assisted ventilation, he was placed in the left lateral decubitus position. After careful skin preparation and draping, the sacral cornua were identified, and a 21-gauge, short bevel, winged needle with tubing was inserted into the sacral canal through the skin overlaying the sacral hiatus. However, because aspiration was positive for blood, the needle was withdrawn and then reinserted into the sacral canal.

Aspiration was then negative for blood, and cerebrospinal fluid, 4.5 ml of 1% lidocaine with 1:200,000 epinephrine, was injected within 45 sec. The patient's heart rate did not change remarkably during these procedures. With completion of injection, however, he developed gasping respiration. He was immediately hyperventilated with 100% oxygen. When he was placed in the supine position, spotty cyanosis was observed on his lips, the thoracic and abdominal wall, and the upper and lower limbs, even though manual ventilation produced appropriate movements of the chest and breath sounds were prominent bilaterally. Systolic blood pressure decreased to 30 from 70 mm Hg, and heart rate also decreased to 60 from 180; finally idioventricular beats developed.

Cardiopulmonary resuscitation and appropriate drug treatments including atropine, 0.1 mg intravenously (iv), epinephrine, 52.5 μ g IV, and 7% sodium bicarbonate, 5 ml IV, were begun immediately. About 5 min after the circulatory collapse, his electrocardiogram showed normal sinus rhythm, and systolic blood pressure increased to 95 mm Hg. Arterial blood gas analysis revealed respiratory, and metabolic acidosis (pH 7.25, PaCO_2 51 mm Hg, PaO_2 355 mm Hg, base excess -6 mEq/L). Two minutes later respirations became spontaneous, and he actively moved both lower and upper limbs. There was no evidence of the motor or sensory blockade that would be expected after the caudal anesthesia. The patient was transferred to the ICU where he was treated with continuous positive airway pressure for 5 hr. An electroencephalogram in the ICU showed no abnormality, and recovery was uneventful. Plasma concentrations of lidocaine were 4.72 μ g/ml 15 min after the injection and 1.40 and 0.87 μ g/ml 2 hr and 3 hr after injection.

Discussion

The most impressive event in this case was the rapid development of idioventricular beats and profound

Received from Institute of Clinical Medicine, University of Tsukuba, and Department of Anesthesiology, University of Tsukuba Hospital, Sakuramura, Ibaraki, Japan. Accepted for publication May 15, 1986.

Address correspondence to Dr. Matsumiya, Institute of Clinical Medicine, University of Tsukuba, Sakuramura, Ibaraki 305, Japan.

circulatory collapse accompanied by the gasping respirations and the spotty cyanosis. We did not observe convulsions after the injection, though the gasping respirations might have been a manifestation of central nervous system stimulatory effects of lidocaine. Because of the very rapid sequence of events and resultant absence of any evidence of block after injection of lidocaine, the event in this case can be considered due to inadvertent injection into the epidural vessels, though the plasma lidocaine levels cannot completely exclude the possibility of epidural injection.

The cardiovascular system is known to be more resistant than the central nervous system to the toxic effects of intravenous lidocaine (5,6). The cardiotoxic dose of lidocaine is approximately four or five times the seizure dose (5,6). Furthermore, in the absence of marked hypoxia or acidosis, serious cardiac arrhythmias appear with supraconvulsant doses of IV bupivacaine but not with IV lidocaine in sheep (7) or cats (8). In dogs anesthetized with pentobarbital, IV lidocaine, 10 mg/kg, does not have a negative inotropic action, though mepivacaine and etidocaine do (9). On the basis of reports such as these, lidocaine, 8 mg/kg, per se is unlikely to have caused the cardiovascular collapse in our case. A possible cause of the adverse reaction described in this case might be either a combined action of lidocaine and halothane or an effect of the epinephrine added to the lidocaine solution. The observation of spotty cyanosis might indicate the potent vasoconstricting action of epinephrine on the skin after the inadvertent intravascular injection.

The incidence of cardiac arrhythmias due to epinephrine is increased during halothane anesthesia (10). Infants, however, apparently can tolerate greater doses of epinephrine than adults can in mg/kg, with fewer arrhythmias during halothane anesthesia (11). Similarly, epinephrine-induced arrhythmias during halothane anesthesia in pigs, did not occur in young pigs (ages 1-3 days), but in older pigs (ages 50-60 days) premature ventricular contractions or ventricular tachycardia resulted when epinephrine was infused for 10 min at $10 \mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$. The arrhythmogenic dose in older pigs was $10.5 \mu\text{g}/\text{kg}$ (12). In our case, if the entire 4.5 ml of lidocaine with epinephrine 1:200,000 was injected intravascularly, $4 \mu\text{g}/\text{kg}$ of epinephrine would have been given.

The cardiovascular toxicity of lidocaine is modified by the existing level of activity of the autonomic nervous system. When the autonomic nervous system is affected by anesthetics, sufficient doses of IV lidocaine can produce depression of myocardial function (13-15). Scott et al. (13) observed a decrease in cardiac output and no change in heart rate after lidocaine,

150 mg IV, in humans during nitrous oxide-halothane anesthesia. In their report, the plasma concentration of lidocaine 3 min after injection ranged from 4.9 to $8.7 \mu\text{g}/\text{ml}$. In our case, although the plasma level of lidocaine immediately after the injection was not determined, it was possible that plasma levels of lidocaine might approach the considerably high concentrations that produce cardiovascular collapse. However, our unpublished observations in dogs anesthetized with halothane showed that 10 mg/kg of plain IV lidocaine does not affect cardiovascular function, whereas 10 mg/kg of lidocaine with 1:200,000 epinephrine IV produces as severe cardiovascular perturbations as observed with epinephrine alone.

It is well-known that the sympathetic nervous system in newborns is relatively immature (16-18). Buckley et al. (16) reported differing rates of postnatal maturation of cardiovascular α - and β -adrenergic mechanisms in swine; perhaps this is the basis of age-related differences in the direction and magnitude of cardiovascular responses to epinephrine. In spite of the age-related differences anticipated in infants, epinephrine has been used successfully to initiate spontaneous cardiac contractions during resuscitation, as we did in the present case, though one may ask why a larger dose ($52.5 \mu\text{g}$) worked beneficially when given during resuscitation, while a smaller dose ($22.5 \mu\text{g}$) caused the cardiovascular collapse in this infant. In addition to the interaction between halothane and epinephrine, the difference may be related to the fact the acidosis that developed after the event might have reduced the responsiveness of the heart to epinephrine (19). However, a residual effect of halothane might also have been present during the resuscitation period. Indeed, in the present case, base excess of -6 mEq/L was reported in spite of the administration of 5 ml of 7% sodium bicarbonate.

It has been reported that accidental intravascular injection could occur after a negative aspiration test for blood in caudal epidural blocks (20,21). In our case the negative aspiration was also unable to preclude the intravascular placement of a needle. Therefore, even for a single injection, we emphasize the importance of close observation of patients for reactions to the test dose of local anesthetic with epinephrine.

In summary, we describe a patient who had circulatory collapse after an inadvertent intravascular injection of 4.5 ml of a solution of 1:200,000 epinephrine in 1% lidocaine. This case suggests that the concurrent administration of epinephrine added to lidocaine is unlikely to protect against the cardiac toxicity due to accidental intravascular injection of local anesthetic, and, furthermore, that the inclusion of epinephrine in lidocaine solutions may even be harm-

Infiltration of a Neuromuscular Relaxant in Diagnosis and Treatment of Torticollis

Eugesse Cremonesi, MD, and Kazuko Nakai Murata, MD

Torticollis, i.e., involuntary and sustained rotation of the head, may be of peripheral or central origin (1,2). The peripheral types are due to irritation of vestibular or spinal pathways and are generally benign. They are not hereditary and often recede when benzodiazepines and other central muscle relaxants are used in combination with physiotherapy. However, this treatment requires several days and may be associated with undesirable side effects, including somnolence and downgrading of intellectual functions. Torticollis due to a central cause, either tonic or phasic, is a striatal disease genetically transmitted and sometimes associated with torsion spasm, which is a progressive, genetically transmitted neural degenerative illness (3). Its treatment, complex and not always effective, consists of stereotactic lesioning of central structures, transection of the spinal nerves that innervate the affected muscles, or high frequency electrical stimulation of the dorsal column of the spinal cord (4).

Identification of the muscles involved in torticollis of central origin is, therefore, of the utmost importance. Usually the muscles are identified by clinical examination, electromyography, and selective blocking of the accessory and C-1 nerves, as well as of the posterior branches of the C-2, C-3 and C-4 roots and of the splenic complex. Blocking of these nerves is understandably difficult due to the extensive overlapping of motor innervation. Infiltration of the cervical plexus is also not useful for the same reason.

The above mentioned difficulties led us to directly infiltrate the muscles involved in torticollis with a local anesthetic. Because neither relief of pain nor a good degree of relaxation were achieved in acutely and chronically affected patients, we decided to infiltrate the muscles with a neuromuscular relaxant. This paper reports the results of selective intramuscular injection of pancuronium bromide, to identify the in-

dividual muscles affected as a diagnostic procedure, to induce relaxation of the muscle involved for therapeutic purposes, and to determine which patients required surgery.

Methods

Ten patients, seven women and three men 22–52 yr old, were studied. Three had had the central type of chronic torticollis with noticeable sternocleidomastoid hypertrophy for months. Seven patients had had acute torticollis for a few days. Five of the seven patients with acute torticollis had been treated with benzodiazepines for 2 days without benefit. The three patients with chronic torticollis had taken several drugs, mostly sedatives, and previously had had 1% lidocaine infiltration of the sternocleidomastoid muscle without relief.

The affected muscles were infiltrated with a solution of pancuronium bromide (2 mg diluted to 20 ml in 0.5% lidocaine). The needle was inserted perpendicularly to the long axis of the muscle, and each of the sites shown in Figure 1 were injected with ± 1 ml of the solution.

In addition to age, sex, race, duration of the disease, and medications being used, the results of neurological examination and functional evaluation of the affected muscles were recorded. Blood pressure, heart rate, and respiratory rates were measured every 5–10 min for 60 min after injection of the pancuronium solution. Side effects such as generalized reduction in muscle tone; difficulty in breathing, swallowing, or speaking; diplopia; and changes of the level of consciousness, as well as the expected effects of the infiltration (local muscular relaxation and pain relief) were carefully assessed. All patients gave informed consent for the procedure as approved by our Medical Institutional Committee.

Results

Except for contracture of cervical muscles, mainly the sternocleidomastoid, the patients had no neurological

Received from the Institute of Psychiatry, Division of Functional Neurosurgery, School of Medicine, University of São Paulo, São Paulo, Brazil. Accepted for publication May 12, 1986.

Address correspondence to Dr. Cremonesi, Terapêutica Clínica, Cx Postal 2921, 01246 São Paulo SP, Brasil.

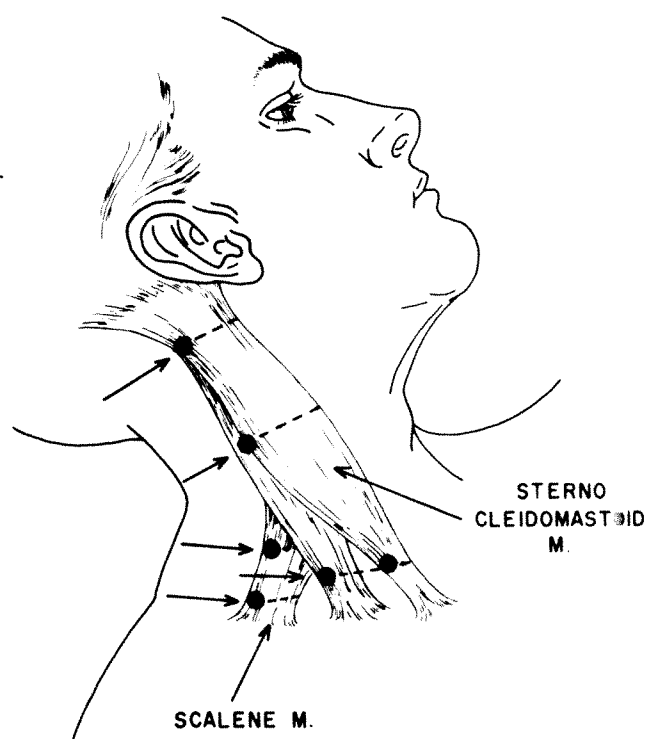


Figure 1. Sites at which injections of lidocaine-pancuronium solution were made in patients with torticollis.

disturbances. During the 60 min after the infiltration, there were no changes in consciousness, blood pressure, heart rate, respiratory rate, general muscle tone, ability to speak, or eye convergence except in one patient in whom a large volume (20 ml) of the pancuronium solution was injected with subsequent development of mild generalized muscular hypotonia, diplopia, and palpebral ptosis for about 30 min.

The total amount of pancuronium used in order to assure complete relaxation of the muscle being infiltrated varied from 0.5 to 2 mg (5–20 ml of the solution), depending upon the degree of contraction and number of muscles involved. Relaxation was complete in the infiltrated muscles in all patients. In patients with chronic torticollis, contracture returned within 2 or 3 hr, but in all patients with acute torticollis, relief was complete and did not recur within the 3-week follow-up period. Neither local muscular dysfunction nor local pain in the injected muscle occurred in the 3 weeks after injection.

Discussion

The local infiltration of pancuronium proved to be highly effective in treatment of acute torticollis. The use of lidocaine with the pancuronium instead of distilled water, prevented the sharp pain that preliminary experiments showed to occur during and immediately after infiltration of the muscle. Lidocaine is well-known to induce vasodilation and may have avoided local vascular spasm provoked by the injection itself and possibly providing a better irrigation of the affected muscles.

The muscular relaxation was complete in infiltrated muscles in all the patients with acute torticollis, i.e., the torticollis was peripheral in origin, and surgery was thus not indicated. In the chronic torticollis the recurrence of symptoms after infiltration is compatible with the more complex central organization of the abnormal head and shoulder postures.

The ease with which this inexpensive procedure can be carried out and permanent abolition of acute torticollis can be achieved by local infiltration with a neuromuscular relaxant suggest that similar injections may be useful in treatment other illnesses in which a local muscular spasm is the main symptom.

In summary, we found that muscle infiltration with a mixture of pancuronium (2 mg in 0.5% lidocaine) in 10 patients with torticollis (acute in seven, chronic in three) immediately relieved muscle spasm and pain in all of them. Relief was still present at the end of the 3-week follow-up period in patients with acute torticollis. Relief lasted only 2–3 hr in patients with chronic torticollis. Side effects, occurring in one patient, were minimal. Local infiltration of muscles in torticollis with a neuromuscular relaxant is useful in diagnosis of the type of torticollis involved and treatment of acute torticollis.

References

1. Molina-Negro P. Functional neurosurgery of abnormal movements. In: Rasmussen T, Marino R. Functional neurosurgery. New York: Raven Press, 1979:89–121.
2. Molina-Negro P. Neurology to brain functional disorder. In: Rasmussen T, Marino R. Functional Neurosurgery. New York: Raven Press, 1979:25–44.
3. Bertrand C, Molina-Negro P, Martinez SN. Combined stereotactic and peripheral surgical approach for spasmodic torticollis. *Appl Neurophysiol* 1978;41:122–33.
4. Gildenberg PL. Treatment of spasmodic torticollis by dorsal column stimulation. *Appl Neurophysiol* 1978;41:113–21.

Total Airway Occlusion and Superior Vena Cava Syndrome in a Child with an Anterior Mediastinal Tumor

Dennis R. Northrip, MD, Bradford K. Bohman, MD, and Kentaro Tsueda, MD

Lymphatic tumors are common neoplasms of the anterior and middle mediastinum in infants and children. Many of the tumors, Hodgkin's disease in particular, are amenable to radiation and/or chemotherapy, and the results of these treatments have continued to improve in recent years. The prognosis and mode of therapy depend on prior knowledge of the diagnosis and extent of the disease. Biopsy of these tumors in various locations and various diagnostic staging procedures have been performed, many under general anesthesia. These diagnostic procedures were originally considered to be safe and to carry only a minimal risk. However, earlier surgical reports suggested that these procedures may be associated with serious perioperative complications (1,2). Since 1973, 15 cases associated with morbidity and mortality secondary to extrinsic compression of the upper airway, heart, and vena cava by anterior mediastinal tumors have been reported, mostly in children (3-11). There were two intraoperative deaths in these reports.

We report an additional death in a child with a large mediastinal tumor who was scheduled for a thoracotomy, and we review briefly the previously reported cases. The child developed a total airway occlusion at induction of anesthesia and severe obstruction of the superior vena cava in the left lateral thoracotomy position.

Case Report

An 11-yr-old girl, 158 cm in height and weighing 36 kg, was admitted because of shortness of breath, non-productive cough, fatigue, anorexia, and a weight loss of 4.5 kg over a 3-week period. For approximately one week, the patient had also noticed puffiness of the face in the morning, which usually disappeared by

noon. On admission, the patient was anxious and mildly dyspneic, preferring to remain in the right lateral position. She was unable to lie supine because of exacerbation of the dyspnea. The patient had been an essentially healthy child until the current illness.

Arterial blood pressure was 117/82 mm Hg, heart rate 148 beats/min, and respiratory rate 22 breaths/min. There was no cyanosis. Slight edema was present in the periorbital area. Excursion of her chest cage was symmetrical, but breath sounds were decreased in the right upper lung fields. There was a grade I/IV systolic murmur at the lower left sternal border. There were no palpable lymph nodes in the neck or supraclavicular fossae. The hemoglobin level was 11.7 g/dl. Serum electrolytes, glucose, blood urea nitrogen, creatinine, albumin, and bilirubin were all within normal limits. Chest roentgenograms showed a large anterior mediastinal mass, prominent right hilum, posteriorly deviated trachea, and atelectasis of the right upper lobe.

On the morning after admission, the patient was scheduled for computerized axial tomography (CAT) and thoracotomy for tissue diagnosis. The CAT was aborted because she was unable to assume the supine position due to exacerbation of dyspnea. The patient was brought to the operating room in the right lateral position directly from the radiology department. She was apprehensive on arrival. Arterial blood pressure was 116/40 mm Hg, heart rate was 102 beats/min and respiratory rate was 26 breaths/min. The patient was given oxygen by mask for approximately 3 min. The ECG was monitored continuously. Blood pressure was measured by a Dinamap with the cuff affixed to the left arm. Anesthesia was induced in the right lateral position with a slow intravenous injection of thiopental, 125 mg. Upon loss of the eyelid reflex, the patient could not be ventilated by mask. The patient was turned supine for tracheal intubation. It was then immediately apparent that the airway was completely occluded. The trachea was rapidly intubated without any difficulty after succinylcholine, 40 mg, given intravenously (IV). However, the airway obstruction

Received from the Departments of Anesthesiology, Kosair-Children's Hospital and the University of Louisville School of Medicine, Louisville, Kentucky. Accepted for publication May 15, 1986.

Address correspondence to Dr. Tsueda, Department of Anesthesiology, University of Louisville, Louisville, KY 40292.

remained total. The endotracheal tube was advanced. The patient was turned to the right lateral position and then to the right lateral semiprone position, but none of these maneuvers established an airway.

The endotracheal tube was removed and a ventilating rigid bronchoscope was inserted in the trachea. The bronchoscopy revealed total occlusion of the lower portion of the trachea and the right mainstem bronchus. The left mainstem bronchus was also partially occluded. After the bronchoscope was advanced through the area of tracheal occlusion down to the carina, faint breath sounds could be auscultated over the left lung fields with inspiratory pressures ranging from 80 to 90 cm H₂O. The arterial blood pressure was 65/40 mm Hg and the pulse rate 60 beats/min. The ECG showed a junctional rhythm. Intravenous ephedrine restored sinus rhythm and improved heart rate and blood pressure. The decision was made to proceed with debulking of the tumor. The ventilatory bronchoscope was left in the trachea.

When the patient was placed in the left lateral position for thoracotomy, cyanosis of the face and upper extremities developed and blood began to flow upward into the IV line. At the same time, arterial blood pressure and heart rate decreased to 58/40 mm Hg and 56 beats/min, respectively; they responded to intravenous epinephrine and bicarbonate. A saphenous vein cutdown was performed. Immediately upon entering the chest, the heart rate decreased to 32 beats/min and the blood pressure was unrecordable. The heart was empty. Cardiac massage was initiated. Ventilation obtained through the bronchoscope did not improve. Only faint breath sounds could be auscultated over the left lung field with high inspiratory pressure. Crystalloid solution and blood were given along with resuscitative drugs, i.e., epinephrine, calcium chloride, and bicarbonate. The tumor was debulked rapidly over the subsequent 45 min, while resuscitation continued. After the debulking, the inspiratory pressure required to ventilate the left lung through the bronchoscope decreased to 30-40 cm H₂O. The cyanosis of the face and upper extremities had disappeared, and the arterial blood pressure and heart rate stabilized at 95/55-110/60 mm Hg and 116-120 beats/min, respectively. The left radial artery was finally successfully cannulated. With an FI_O₂ of 1.0, the pH was 7.43; PaCO₂ was 23 mm Hg; and PaO₂ was 370 mm Hg. After careful hemostasis the chest was closed. The ventilating bronchoscope was then replaced with a Robert-Shaw double-lumen endotracheal tube after the patient was placed in the supine position. The right lung remained unventilated.

The patient never regained consciousness. The EEG

showed no cerebral activity on the sixth postoperative day; and she died on the seventh postoperative day. The family did not give permission for an autopsy. The tissue diagnosis was histiocytic lymphoma.

Discussion

Anesthetic morbidity and mortality associated with large anterior mediastinal tumors in the 15 reported cases cover the whole spectrum of airway obstruction and cardiovascular compression. Two children, admitted in near asphyxiation, were resuscitated with endobronchial intubation, but both patients died in the intensive care unit from sepsis and massive hemorrhage, respectively (3,5). The remaining 13 patients underwent diagnostic procedures under general anesthesia. Complications developed either immediately after induction of anesthesia or in the immediate postoperative period. A total or near total airway obstruction occurred in five of these patients (4,7,10,11). One patient died immediately after induction of anesthesia (11). In three patients, the total airway occlusion was related to apnea and depth of anesthesia at induction, and resumption of spontaneous breathing reestablished the airway patency in two patients (4,10). Insertion of a longer endotracheal tube and ventilating bronchoscope past the area of obstruction reestablished an airway in the other two patients (7,10). In seven out of the eight remaining patients, the extent of airway obstruction ranged from occlusion of a mainstem bronchus after induction of anesthesia to a lobar atelectasis in the postoperative period.

Symptoms consistent with cardiovascular compression have been reported less frequently. One patient, who did not tolerate the supine position and in whom anesthesia was thus induced in the sitting position, developed cardiac arrest immediately after being placed in the supine position (9). There was no airway obstruction in this patient, and death was attributed to further compression of the heart by the tumor that had infiltrated the pericardium. The superior vena cava syndrome developed in two patients during operation (4,6).

The morbidity and mortality in these reported cases do not appear to be related to preoperative respiratory symptoms and roentgenographic evidence of airway compromise. In patients with upper airway obstruction, the changes in maximum voluntary ventilation (MVV) are minimal if the area of occlusion is 50% or less. Miller and Hyatt described a patient with stridor on deep inspiration who was asymptomatic on normal breathing. The MVV was 14% of predicted, and the upper airway was more than 90% occluded with

a lesion (12). Preoperative respiratory symptoms in the five patients who developed a total or near total airway occlusion at induction of anesthesia were often mild and ranged from no symptoms (4); to dyspnea on exertion, i.e., playing football (11); to intolerance of the supine position (10). Narrowing or deviation of the mediastinal airway was demonstrated roentgenographically in two of these patients. In one patient, a chest roentgenogram was normal. In two patients, roentgenographic findings were not documented. Of the remaining eight patients, only three had roentgenographic evidence of an airway that was compromised.

Intolerance of the supine position or other positions in patients with a large anterior mediastinal tumor indicates that in these patients the weight of the tumor on the airway, major vessels, and heart increases in certain positions, creating a critical narrowing of the airway and/or obstruction to venous return. Such intolerance was documented in three of the reported cases. One patient, who was resuscitated from asphyxia with a tracheal intubation on admission, died in the intensive care unit without ever undergoing a diagnostic operation (13). Another patient died of cardiac compression immediately after induction of anesthesia (9). A total airway occlusion developed immediately after tracheal intubation in the patient who survived and was relieved only after insertion of a rigid bronchoscope in the trachea past the area of obstruction and turning the patient to the right lateral semiprone position (10). Thus intolerance of the supine position appears to be associated with serious complications and carries a grave prognostic significance for patients with mediastinal tumors.

The superior vena cava syndrome occurs more frequently in patients with diffuse histiocytic lymphoma than in those with Hodgkin's disease and other lymphomas. It is more frequently associated with lesions on the right side and obstruction below the azygous channel (14). Two patients had facial edema on admission, i.e., a finding consistent with the superior vena cava syndrome. Both patients died. One of the two patients was admitted asphyxiated (3). The other developed total occlusion of the airway at induction of anesthesia. The tumor had infiltrated both pericardium and myocardium in this patient. Thus facial edema, although an early symptom of the superior vena cava syndrome, may also be related to other serious complications, e.g., severe airway occlusion at induction of anesthesia and tumor involvement of the heart.

As tumors increase in size, the trachea and mainstem bronchi as well as the major vessels may be

exposed to an increasingly positive pressure. When the transmural pressure of the airway and the superior vena cava exceeds the elastic recoil of the wall of these structures, extrinsic compression develops (15). With induction of anesthesia, the diaphragm shifts cephalad, and a substantial decrease in functional residual capacity occurs, presumably due to a decrease in the inherent tone of the diaphragm and intercostal muscles (13). Thus transmural pressure increases as pleural pressure becomes less negative, and a further compression could occur with induction of anesthesia. In addition, inhalation anesthetics, as well as thiopental, decrease smooth muscle tone of both vessels and airway (16), resulting in decrease of the elastic recoil. The symptoms of tumor compression of mediastinal structures were evident on admission in our patient. The chest roentgenograms were consistent with a large anterior mediastinal tumor located predominantly in the right side, i.e., a prominent right hilum and atelectasis of the right upper lobe. The patient had had facial edema for approximately one week, and she was unable to lie in any position other than the right lateral position because of severe dyspnea.

In our case, total airway occlusion promptly followed the loss of consciousness. The maneuvers successfully employed in the previous reports, i.e., advancement of the endotracheal tube (7) and the right lateral semiprone position (10), did not relieve the airway occlusion in our patient. A rigid bronchoscope advanced past the area of obstruction in the trachea established a minimal airway patency, and only faint breath sounds could be auscultated over the left lung fields with the inspiratory pressure in excess of 80 cm H₂O. This severe airway compromise continued until debulking of the tumor was completed. The severe superior vena cava syndrome that developed on turning the patient into the left lateral position became worse on opening the chest, suggesting that further tumor compression of the superior vena cava occurred when the negative pleural pressure that held the tumor away from the vessel was lost. The heart was empty, and severe bradycardia and hypotension that required a prolonged resuscitation ensued. The superior vena cava syndrome persisted until the tumor was debulked. The episode caused cerebral death in our patient.

A survey by Piro et al. of patients with Hodgkin's disease undergoing staging laparotomy demonstrated that perioperative airway complications are related to the size of tumors within the chest (7). However, airway abnormality could not be demonstrated by preoperative roentgenographic examina-

tions in three out of five patients who developed airway complications in their series. The absence of symptoms does not preclude serious complications (4). Diagnostic procedures in patients with a large anterior mediastinal tumor seem best performed under local anesthesia whether the symptoms are present (9,11) or not. However, if superficial nodes are not palpable, the child does not tolerate diagnostic procedures under local anesthesia, the biopsy result is inconclusive, the tumor is benign, or the tumor is both radioinsensitive and chemoinensitive, an operative procedure under general anesthesia is required for tissue diagnosis, excision or debulking. It has been recommended that anesthesia be induced in the lateral semi-Fowler position, to avoid muscle relaxants and to maintain spontaneous breathing (4,9-11). This approach would enable the anesthesiologist to assess whether occlusion of the airway related to the depth of anesthesia might occur and, if it occurs, to lighten anesthesia. Once a total airway occlusion develops, there appears to be no reliable maneuver to reestablish an airway. Neuman et al. recommend a partial cardiopulmonary bypass standby during induction of anesthesia in symptomatic patients (11). The reported deaths appear to have occurred rapidly after the induction of anesthesia. In our patient, a sequence of almost inevitable events followed in rapid succession. Partial cardiopulmonary bypass would provide a protection against total airway occlusion (17), but we feel that its efficacy in the presence of severe superior vena cava obstruction remains to be demonstrated.

The operative procedure required for tissue diagnosis is, when performed under general anesthesia, associated with life-threatening complications in patients with large anterior mediastinal tumors. Once the complications develop, the death rate appears to be high. We feel, as others have earlier (3,9,16,18), that the risks of general anesthesia far outweighs the benefit of tissue diagnosis in symptomatic patients, particularly those with obvious evidence of tumor compression of mediastinal structures; therefore, serious consideration should be given to empirical radiation and/or chemotherapy prior to tissue diagnosis.

References

1. Olumide AA, Osunkoya BO, Ngu VA. Superior mediastinal compression: a report of five cases caused by malignant lymphoma. *Cancer* 1971;27:193-202.
2. Meeker WR Jr, Richardson JD, West WO, Parker JC. Critical evaluation of laparotomy and splenectomy in Hodgkin's disease. *Arch Surg* 1972;105:222-9.
3. Amaha K, Okutsu Y, Nakamura Y. Major airway obstruction by mediastinal tumor. *Br J Anaesth* 1973;45:471-2.
4. Bittar D. Respiratory obstruction associated with induction of general anesthesia in a patient with mediastinal Hodgkin's disease. *Anesth Analg* 1975;54:399-403.
5. Todres ID, Reppert SM, Walker PF, Grillo HC. Management of critical airway obstruction in a child with a mediastinal tumor. *Anesthesiology* 1976;45:100-2.
6. Tonnesen AS, Davis FG. Superior vena cava and bronchial obstruction during anesthesia. *Anesthesiology* 1976;45:91-2.
7. Piro AJ, Weiss DR, Hellman S. Mediastinal Hodgkin's disease: a possible danger for intubation anesthesia. *Int J Radiat Oncol Biol Phys* 1976;1:415-9.
8. Gutman JA, Jacob IH. Mediastinal tumor presenting as a new heart murmur: diagnosis and treatment. *J Med Soc NJ* 1979;76:364-6.
9. Keon TP. Death on induction of anesthesia for cervical node biopsy. *Anesthesiology* 1981;55:471-2.
10. Bray RJ, Fernandes FJ. Mediastinal tumor causing airway obstruction in anaesthetised children. *Anaesthesia* 1982;37:571-5.
11. Neuman GG, Weingarten AE, Abramowitz RM, Kushins LG, Abramson AL, Ladner W. The anesthetic management of the patient with an anterior mediastinal mass. *Anesthesiology* 1984;60:144-7.
12. Miller RD, Hyatt RE. Obstructing lesions of the larynx and trachea: clinical and physiologic characteristics. *Mayo Clin Proc* 1969;44:145-61.
13. Froese AB, Bryan AC. Effects of anesthesia and muscle paralysis of diaphragmatic mechanics in man. *Anesthesiology* 1974;41:242-55.
14. Lokich JJ, Goodman R. Superior vena cava syndrome. *JAMA* 1975;231:53-61.
15. DeGraff AC Jr, Bouhuys A. Mechanics of air flow in airway obstruction. *Ann Rev Med* 1973;24:111-31.
16. Fletcher SW, Flacke W, Alper MH. The actions of general anesthetic agents on tracheal smooth muscle. *Anesthesiology* 1968;29:517-22.
17. Wilson RF, Steiger Z, Jacobs J, Sison OS, Holsey C. Temporary partial cardiopulmonary bypass during emergency operative management of near total tracheal occlusion. *Anesthesiology* 1984;61:103-5.
18. Crone RK, O'Rourke PP. Pediatric and neonatal intensive care. In: Miller RD, ed. *Anesthesia*. New York: Churchill Livingstone, 1986:2392.

Junctional Rhythm Can Mimic Air Embolism during Precordial Doppler Monitoring

Said S. Azad, MD, David Maguire, MD, and Michael E. Goldberg, MD

Venous air embolism (VAE) is a recognized complication of neurosurgical procedures performed in the sitting position. Although less common, VAE may also occur in the prone, supine, and lateral positions (1). Monitoring of precordial Doppler heart sounds has been advocated for early detection of venous air embolism (2). The following case report describes how a change in precordial Doppler sounds produced by a junctional rhythm may mimic those caused by VAE.

Case Report

A 65-yr-old, 75 kg male was scheduled for posterior fossa craniotomy for marsupialization of a subarachnoid cyst. Past medical history included Type II diabetes mellitus, mild chronic obstructive pulmonary disease, and arthritis. Medications at the time of surgery included oxybutynin and ibuprofen. Physical examination was unremarkable. Preoperative laboratory values, chest roentgenogram, and electrocardiogram were within normal limits.

The patient was premedicated with morphine, 8.0 mg, and atropine, 0.4 mg intramuscularly (IM). He was brought to the operating room where a 16-gauge peripheral IV 20-gauge left radial artery catheter, and a 16-gauge central venous pressure (CVP) catheter were inserted through the right brachial vein. ECG showed normal sinus rhythm. Additional monitoring included precordial Doppler (Versatone Model D8) heart sounds over the right fourth intercostal space and after induction of anesthesia, end tidal CO₂ (ETCO₂) (Datex Puritan-Bennett Corporation).

After preoxygenation and 6 mg IV *d*-tubocurarine, anesthesia was induced intravenously with 5 mg/kg of thiopental, with administration of 1 mg/kg IV lidocaine, followed by 100 mg IV succinylcholine to fa-

cilitate tracheal intubation. Anesthesia was maintained with 60% nitrous oxide/40% oxygen; isoflurane, 0.5–2% inspired concentration; pancuronium; and fentanyl, 50–100 µg as needed. The patient was in the prone position during surgery.

During the craniotomy, a change from high to low pitch in Doppler sounds was suddenly noted by the anesthesia and neurosurgical staff. VAE was suspected; N₂O was discontinued, and the surgical field was flooded with saline. No air could be aspirated from the CVP. ETCO₂ did not change significantly (–2 torr). However, CVP increased by 4 torr, and systolic BP decreased from 150 mm Hg to 110 mm Hg. It was then noted that a junctional (nodal) rhythm had developed, as evidenced by the absence of P waves on the ECG and Cannon A waves on the CVP (Fig. 1). The combination of abnormal Doppler sounds (despite appropriate action to prevent air entry at the operative site), increased CVP, and decreased blood pressure without a change in ETCO₂ led us to postulate that the abnormal Doppler sounds were secondary to the change to junctional rhythm, and not VAE. To confirm our hypothesis, anesthesia was lightened by decreasing the inspired concentration of isoflurane from 1.5% to 0.75%. The cardiac rhythm then reverted to sinus rhythm with return of Doppler heart sounds to normal, an increase in systolic blood pressure from 110 mm Hg to 150 mm Hg, and a decrease in CVP of 4 torr (Fig. 2). We then attempted to induce nodal rhythm once again by increasing the inspired concentration of isoflurane to 2%. Once again junctional rhythm developed, accompanied by the same changes in Doppler sounds, CVP, and blood pressure. Air could not be aspirated from the CVP, and ETCO₂ did not change.

Discussion

VAE can occur in the sitting, prone, lateral, and supine positions any time that the gravitational gradient between the operative site and right atrium exceeds five centimeters (1). Monitoring of precordial Doppler

Received from the Department of Anesthesiology, Jefferson Medical College of Thomas Jefferson University, Philadelphia, Pennsylvania. Accepted for publication May 12, 1986.

Address correspondence to Dr. Goldberg, Department of Anesthesiology, Jefferson Medical College of Thomas Jefferson University, 111 South 11th Street, Philadelphia, PA.

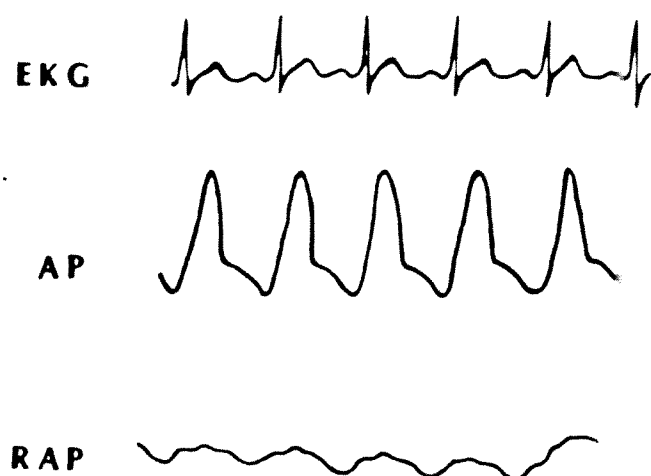


Figure 1. Junctional rhythm and Cannon A waves.

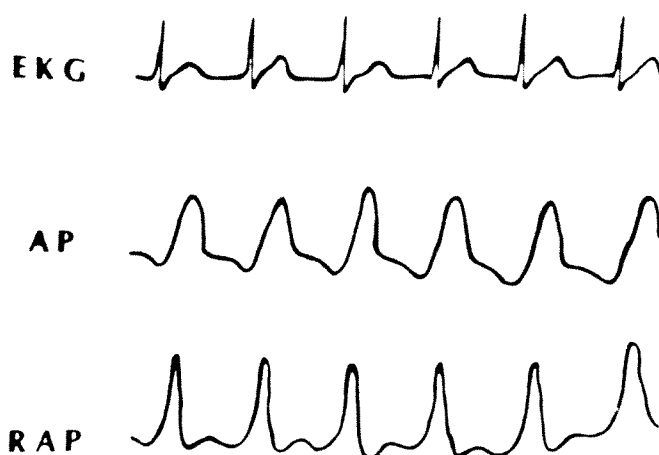


Figure 2. Reversion to normal sinus rhythm with lack of Cannon A wave.

heart sounds has been advocated for early detection of VAE with changes in these sounds attributed to increased echogenicity (2) of air as compared to blood or turbulent flow (3). The detection by Doppler of turbulence caused by injection of heparinized saline through the CVP has indeed been described as a means of ensuring proper placement of the precordial Doppler (4).

During this case, a change in Doppler sounds occurred, and treatment of a suspected VAE was undertaken. We were unable to aspirate air from the CVP, nor was there a significant change in ETCO_2 . The abnormal Doppler sounds persisted with a decrease in blood pressure, and we therefore feel that the events can be explained by the development of junctional rhythm.

Atrial arrhythmias and junctional rhythm can occur during anesthesia with inhalation agents. With the development of junctional rhythm, atrial contraction is lost, resulting in a 20% reduction in cardiac output as seen in patients with ventricular pacemakers (Pacemaker syndrome) (5). Assuming no change in systemic vascular resistance, then a 20% reduction in cardiac output might be expected, resulting in a lower blood pressure (6).

The development of a junctional rhythm in our patient was accompanied by Cannon A waves on the CVP tracing, indicating right atrial contraction against a closed tricuspid valve resulting in turbulence within the right atrium. As Tinker et al. (4) have demonstrated, turbulent flow can cause changes in the Doppler sounds. Because abnormal sounds occurred with the onset of junctional rhythm, returned to normal

with conversion to normal sinus rhythm, and recurred with the subsequent return of junctional rhythm, the abnormal sounds were most likely secondary to turbulence generated by the junctional rhythm.

In summary, we present a case where the development of abnormal Doppler sounds in a patient undergoing posterior fossa craniotomy in the prone position was due to junctional rhythm and not VAE. Factors supporting this contention include the development of abnormal Doppler sounds, junctional rhythm, increased CVP, and decreased blood pressure without a change in ETCO_2 . This case supports the contention that precordial Doppler, although very sensitive for detecting VAE, should not be used alone, but in combination with clinical signs and other monitoring devices to detect venous air embolism.

References

1. Newfield P. Anesthesia for posterior fossa procedures. In: Cotrel JE, Turndorf H, eds. *Anesthesia and neurosurgery*. St. Louis: The C.V. Mosby Company, 1980:168-82.
2. Michenfelder JD, Miller BH, Gronert GA. Evaluation of an ultrasound device (Doppler) for the diagnosis of venous air embolism. *Anesthesiology* 1972;36:164-7.
3. Maroon JC, Goodman JM, Hornert G, Campbell RL. Detection of minute venous air emboli with ultrasound. *Surg Gyn Obstet* 1968;127:1236-8.
4. Tinker JH, Gronert GA, Messick JM, Michenfelder JD. Detection of air embolism, a test for positioning of right atrial catheters and Doppler probe. *Anesthesiology* 1975;43:104-6.
5. Erbel R. Pacemaker syndrome. *Am J Cardiol* 1979;44:771-2.
6. Forland JM, Schweiss JF. Pacemaker syndrome during anesthesia. *Anesthesiology* 1984;60:588-90.

Spontaneous Cardiac Herniation after Pneumonectomy

Chris M. Weinlander, MD, Martin D. Abel, MD, and Jeffrey M. Piehler, MD

Cardiac herniation through a pericardial defect created at the time of pneumonectomy is potentially life-threatening (1,2). This case report is offered as a reminder, given the number of previous references (1-10), that cardiac herniation after pneumonectomy most commonly presents in the perioperative period when the patient is still under the immediate care of an anesthesiologist. It should be included in the differential diagnosis of cardiovascular decompensation after pneumonectomy. Factors that may contribute to this complication include suction applied to the evacuated hemithorax, positioning the patient with the operative side dependent, positive-pressure ventilation, and coughing or vomiting (3,4,5). Clinical findings are variable, ranging from isolated x-ray abnormalities to sudden hypotension, atrial and ventricular dysrhythmias, superior vena caval syndrome, and cardiovascular collapse (6,7,8,9). We report a case in which invasion of the superior vena cava (SVC) by squamous cell carcinoma (SCC) of the lung required resection of a portion of the wall of that vessel followed by a primary repair. In the immediate postoperative period, hypotension and the appearance of findings consistent with a superior vena caval syndrome were initially attributed to stenosis of the SVC. This obscured the correct diagnosis of cardiac herniation after right pneumonectomy, which was subsequently identified and corrected.

Case Report

A 52-yr-old woman was scheduled for a right thoracotomy and possible right upper lobectomy for SCC of the lung. She had a 2-week history of scant hemoptysis and was otherwise healthy. The patient had a history of smoking 1½ packs of cigarettes per day for the previous 30 yr. She was taking no medication. Physical examination was unremarkable. Preopera-

tive laboratory values, including arterial blood gas results, were in the normal range. Chest roentgenogram revealed a 5-cm mass in the right upper lobe hilar region. Pulmonary function tests were consistent with mild obstructive pulmonary disease.

After pretreatment with morphine sulfate, 2 mg, diazepam, 5 mg, and glycopyrrolate, 0.2 mg, anesthesia was induced with thiopental, 250 mg, and muscle relaxation was obtained with atracurium, 50 mg. Laryngotracheal lidocaine spray (120 mg) was administered, and a 35 French left double lumen endobronchial tube (National Catheter Corporation) was placed. Correct position of the endobronchial tube was verified both by auscultation and visualization with a pediatric bronchoscope. A radial artery catheter was inserted. A digital pulse oximeter (Nellcor) was used to monitor hemoglobin oxygen saturation.

The patient was then turned to the left lateral decubitus position. Proper positioning of the endobronchial tube was again verified. Anesthesia was maintained using 100% oxygen, 0.5-1% enflurane, morphine sulfate, diazepam, and atracurium. Pulmonary ventilation was controlled.

The right lung was allowed to deflate passively to facilitate the surgical approach just prior to opening the chest cavity. The patient was well oxygenated throughout the procedure. The tumor mass was found to involve the right upper lobe and to extend through the hilum into the superior vena cava just beneath the entry of the azygous vein. A right pneumonectomy was performed. The point of fixation of the tumor to the superior vena cava was isolated. A tangential clamp was placed across the point of attachment to the vena cava. The attachment was divided, and the caval defect was closed primarily. Although the caval diameter was estimated to be approximately half that noted at the outset, the absence of facial venous suffusion suggested that this was clinically satisfactory. A 3-cm defect had been created high in the pericardium adjacent to the caval resection. This was left open due to its small size and high location, and the procedure was completed without incident. The anesthetic course was uneventful. Vital signs remained stable throughout with a blood pressure of

Received from the Departments of Anesthesiology and Cardiothoracic Surgery, Mayo Clinic, Rochester, Minnesota. Accepted for publication May 12, 1986.

Address correspondence to Dr. Weinlander, Department of Anesthesiology, Mayo Clinic, Rochester, MN 55905.

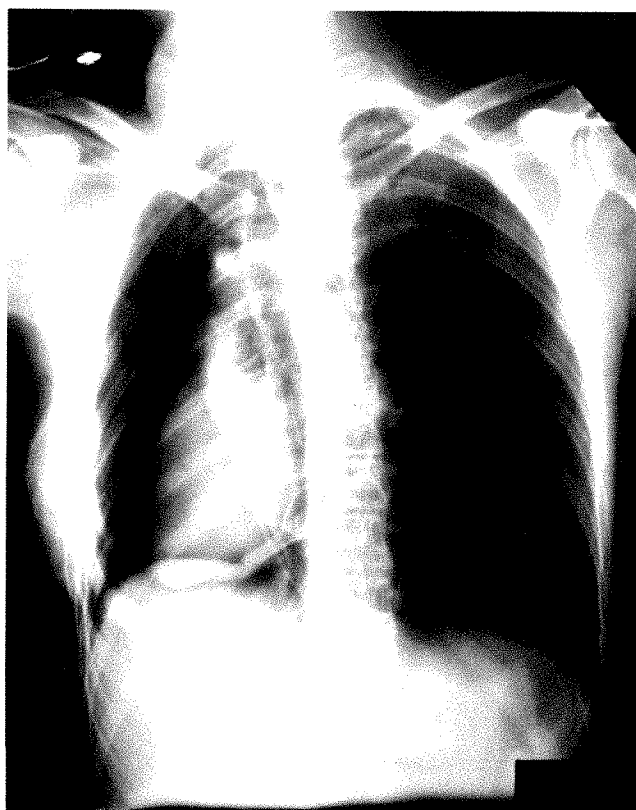


Figure 1. Postoperative chest roentgenogram showing herniation of the heart into the right hemithorax.

•115–130/70–80 mm Hg and a heart rate of 85–100 beats/min.

After completion of surgery, neostigmine, 3 mg, and atropine, 1.2 mg, were given to reverse the muscle relaxation, and spontaneous ventilation was allowed to resume. The patient was extubated in the left lateral decubitus position without difficulty. She did not cough on extubation. A thoracostomy tube connected to an underwater seal that had been inserted during the closure of the chest was then removed. Suction had not been applied to the evacuated hemithorax at any time. She was then turned to the supine position. She was ventilating well spontaneously with a blood pressure of 120/70 mm Hg and a heart rate of 95 beats/min.

She was transferred from the operating table to a transport cart. At that time, she was noted to have a slight decrease in systolic blood pressure to 110 mm Hg with a heart rate of 100 beats/min. A supine chest roentgenogram was obtained on the way to the recovery room. A period of approximately 2 min had elapsed between leaving the operating room and arrival in the radiology suite. In that interval, the patient's systolic blood pressure had decreased to 80 mm Hg. The heart rate had increased to 110 beats/min. A

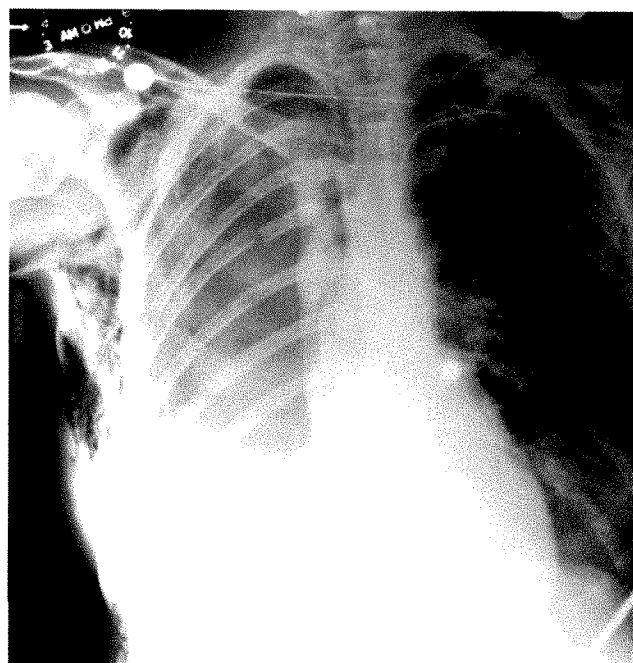


Figure 2. Chest roentgenogram taken on the second postoperative day. The appearance of the thoracic contents is typical of a post-operative right pneumonectomy. The heart has returned to the normal position. There is a pleural effusion on the right.

dusky appearance to her face, neck, and upper torso was noted. The external jugular veins were distended. She was agitated and complained of shortness of breath. Ephedrine, 12.5 mg, was given and the blood pressure increased to 90/40 mm Hg. The chest roentgenogram showed that the heart had herniated into the right hemithorax (Fig. 1).

She was placed in the left lateral decubitus position and returned to the operating room immediately. The blood pressure was noted to increase to 100/40 mm Hg with a heart rate of 110 beats/min on assuming the left lateral decubitus position. The patient remained agitated, and she received another 12.5-mg bolus of ephedrine. The blood pressure increased to 110/60 mm Hg with a heart rate of 115 beats/min.

She was anesthetized with etomidate, 10 mg, and tracheal intubation was carried out in the left lateral decubitus position using 100 mg of succinylcholine. A single lumen 8.0-mm internal diameter endotracheal tube was placed without difficulty. Anesthesia was maintained with oxygen and 0.5% enflurane. The right chest was reopened and the cardiac herniation was found to have reduced spontaneously through the pericardial defect. The blood pressure at this time was 120/70 mm Hg, and the heart rate was 90 beats/min. The upper body suffusion and venous distension resolved. The pericardial defect was closed primarily.

A pulmonary artery catheter was inserted through

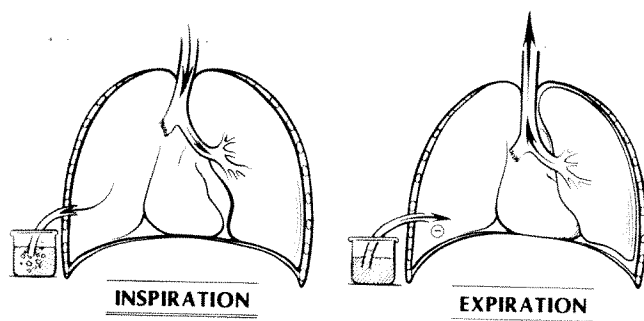


Figure 3. Proposed mechanism for the development of negative intrathoracic pressure in the evacuated hemithorax during positive pressure ventilation. During the inspiratory phase, the mediastinal structures are shifted toward the right, displacing air through the thoracostomy tube. The underwater seal subsequently prevents the air from reentering the hemithorax during the expiratory phase. A small negative pressure in the evacuated hemithorax develops.

the right internal jugular vein. The passage of the catheter was directly visualized by the surgeon as it traversed the SVC. No pressure gradient was observed across the previously resected and narrowed portion of the SVC.

The patient was extubated 1 hr postoperatively. The pulmonary artery catheter was removed the next day, and the patient made an uneventful recovery. A postextubation chest x-ray is shown in Figure 2.

Discussion

This case report is offered as a reminder that cardiac herniation after pneumonectomy is a grave complication that can present itself suddenly to the anesthesiologist. It commonly occurs in the immediate postoperative period (1,2,3), although it may occur several days after operation (10). Herniation leads to obstruction of venous return and may progress to strangulation of the heart in the pericardial defect. In our patient, this complication occurred without application of suction to the pleural cavity, vomiting, coughing, or positioning with the operative side dependent. Prior to extubation, positive pressure ventilation and the placement of the thoracostomy tube to an underwater seal may have allowed the development of a small negative intrathoracic pressure (Fig. 3). During inspiration, expansion of the left lung would cause the mediastinal contents to shift slightly to the right, displacing air from the empty hemithorax through the thoracostomy tube. During expiration, the underwater seal would prevent the reentry of air into the right hemithorax when the mediastinal contents shifted toward their former position. A small amount of negative pressure could develop in the evacuated hemithorax without placing the thoracos-

tomy tube to suction. Although hemodynamic compromise did not occur until well after extubation and removal of the thoracostomy tube, a small negative intrathoracic pressure could have contributed to cardiac herniation.

The clinical findings consistent with superior vena caval syndrome were initially attributed in this case to stenosis or thrombosis of the SVC following resection of a portion of its wall. The correct diagnosis of cardiac herniation was made by chest roentgenogram, however. In order to determine whether a significant superior vena caval obstruction remained, a pulmonary artery catheter was inserted and failed to reveal a pressure gradient across the stenotic area in the SVC. The upper body suffusion resolved after reduction of the heart to its normal position. Although placing the patient in the left lateral decubitus position after the diagnosis was made resulted in some improvement in hemodynamic status, normal hemodynamic parameters returned only with reduction of the heart.

This case serves to illustrate a potentially life-threatening complication that is likely to be confronted in the immediate perioperative period. Cardiac herniation may occur towards the end of surgery, while the dressing is being applied, after extubation, or on the way to the recovery room. Although it has been well-described in the past, in this case the factors that have been reported to contribute to its occurrence were avoided. Despite these precautions, the heart herniated through a small pericardial defect. In addition, resection of a portion of the wall of the superior vena cava obscured the diagnosis until the chest roentgenogram was obtained.

Cardiac herniation should be considered in the differential diagnosis of hypotension, dysrhythmias, superior vena caval syndrome, or cardiovascular collapse after pneumonectomy whenever the pericardium has been entered. Vigilance coupled with an awareness of this serious complication are essential to its diagnosis. If the hemodynamic status of the patient permits, a portable chest roentgenogram will confirm the diagnosis, as it did in our case. Immediate treatment should include positioning with the nonoperative side dependent, avoiding increased inspiratory pressures, and consideration of the injection of air into the evacuated hemithorax. Vasopressor support may also be useful when hemodynamic instability is present. Definitive treatment requires prompt surgical intervention.

The authors thank Julie Vogen for manuscript preparation, Susan Balich for the medical illustrations, and Dr. Kai Rehder for his advice and helpful suggestions.

References

1. Kirchhof AC. Herniation of the heart. Report of a case. *Anesthesiology* 1951;12:774.
2. Gravel JA. Herniation of the heart—a hazard of thoracic surgery: report of two fatal cases. *Can J Surg* 1966;9:72-3.
3. Yacoub MH, Williams WG, Ahmad A. Strangulation of the heart following intrapericardial pneumonectomy. *Thorax* 1968;23:261-5.
4. Patel DR, Schrivastav R, Sabety AM. Cardiac torsion following intrapericardial pneumonectomy. *J Thorac Cardiovasc Surg* 1973;65:626-8.
5. Hidvegi RS, Abdulnour EM, Wilson JAS. Herniation of the heart following left pneumonectomy. *J Can Assoc Rad* 1981;32:185-7.
6. Higginson JF. Block dissection in pneumonectomy for carcinoma. *J Thorac Cardiovasc Surg* 1953;25:582-99.
7. Seltzer JL. Cardiac arrest following pneumonectomy after pericardiotomy. *Anesth Analg* 1978;57:501-3.
8. McKlveen JR, Urgena RB, Rossi NP. Herniation of the heart following radical pneumonectomy: a case report. *Anesth Analg* 1972;51:680-3.
9. Cassorla L, Katz JA. Management of cardiac herniation after intrapericardial pneumonectomy. *Anesthesiology* 1984;60:362-4.
10. Wright MP, Nelson C, Johnson AM, McMillan IKR. Herniation of the heart. *Thorax* 1970;25:656-64.

Letters to the Editor

A Method for Monitoring Pulse Rate Changes during Test Doses of Epidural Anesthetic Solutions in Obstetrics

To the Editor:

The use of epinephrine-containing local anesthetics (3 ml 1:200,000) for test dosing epidural anesthetic injections is commonly practiced. However, monitoring patients for changes in heart rate in the labor suite with an electrocardioscope may be cumbersome. Although some anesthesiologists rely on a nurse to monitor the pulse, this method may be unreliable for detection of a transient tachycardia. ECG monitors are expensive and large; in some centers an ECG monitor is wheeled from one labor room to another, but this is inconvenient and may add to space problems that already exist in crowded labor rooms.

We recently began using a portable pocket size pulse meter (AMEREC 130 Pulsemeter, Amerrec Corporation, PO Box 3825, Bellevue, WA 98009) with good results. The pulse meter utilizes a nontraumatic clip-on sensor that attaches to the patient's ear lobe. It has a cord long enough for the anesthesiologist to easily place the monitor within viewing distance during the initial epidural injection or when subsequently administering epidural medication through an indwelling catheter. The pulse rate is continuously displayed on a $\frac{3}{4} \times 2$ " screen (Fig. 1) with a flashing symbol and a digital rate display. After each use, the battery-operated pulse meter is easily disconnected and conveniently stored in a block cart drawer or jacket pocket awaiting its next use. This monitor costs a small fraction of the cost of either a standard ECG monitor or the Microcor ECG monitor, described in a previous communication (1).

Don Daniels, MD
Letterman Army Medical Center
Department of Anesthesia

Mark A. Rosen, MD
Departments of Anesthesiology, Obstetrics, Gynecology
and Reproductive Sciences
University of California, San Francisco
San Francisco, CA 94143

Reference

1. Diehl PJ, Loeser EA. ECG monitoring with an advanced, truly portable electrocardioscope. *Anesthesiology* 64:1986:301-2.

Midazolam as an Intravenous Induction Agent in the Elderly

To the Editor:

If one were to read only the conclusions of the useful study of Dr. Kanto et al. (1), it might be concluded that 0.15 mg/kg is adequate for induction of anesthesia in the elderly, but this is only true in adequately premedicated subjects. In the absence of premedication we found (2) that even 0.3 mg/kg would not consistently induce anesthesia in fit elderly patients. It was more effective in the elderly than in the young, but only 94% of our patients ($n = 69$) aged 50 yr and over had lost contact with their surroundings by 3 min after this larger dose.

Kanto et al. comment that the "time for induction was rather long." In the above study we convincingly demonstrated an inverse relationship between the age of patients and time to onset of action, which makes it a much more acceptable drug in the elderly. This delay in onset of action makes it difficult to titrate the dose against the patients' needs, especially when one is used to rapidly acting induction agents and a rapid turnover of cases.

Kanto et al. concluded that the more marked clinical effects of midazolam in the elderly, as compared with young patients, can be explained on a pharmacodynamic rather than a pharmacokinetic basis, but this too is only partially true. An increased elimination half-life in elderly patients has been demonstrated for a number of benzodiazepines, including midazolam (3). More relevant to the present study is the direct relation between onset time and plasma al-



Figure 1. Amerrec Pulsemeter 130, showing digital heart rate display.

bumin concentration as demonstrated both by ourselves (4) and by Reves et al. (5). With a highly protein-bound drug like midazolam, minor fluctuations in plasma protein levels could lead to marked changes in the amount of free, and thus pharmacologically active, midazolam.

As the result of routine hospital screening, we have data on over 30,000 consecutive, unselected patients (Fig 1.) that show a general trend for lower plasma proteins in elderly patients. This could explain the more rapid onset of action of midazolam in patients over 50 yr of age.

In reviewing all our pharmacokinetic data on midazolam (over 200 patients studied), we also found that about 5% showed an abnormally prolonged elimination half-life. This applied to patients of all ages, $t_{1/2}$ being in the region of 8-12 hr or even longer (6). Although this may not be clinically important with single small doses when redistribution produces therapeutically low plasma levels, this may not be the case with higher doses or with infusions, where elimination processes assume greater importance.

While we do not wish to detract from the findings of Kanto's study, we feel that consideration of these additional points will make midazolam a safer drug for use in elderly patients.

John W. Dundee, MD
N. James Halliday, FFARCS
Kenneth W. Harper, FFARCS
Department of Anaesthetics
The Queen's University of Belfast
Belfast BT9 7BL
Northern Ireland

References

1. Kanto J, Aaltonen J, Himberg J-J, Hovi-Viander M. Midazolam as an intravenous induction agent in the elderly: a clinical and pharmacokinetic study. *Anesth Analg* 1986;65:15-20.
2. Dundee JW, Halliday NJ, Loughran PG, Harper KW. The influence of age on the onset of anaesthesia with midazolam. *Anaesthesia* 1985;40:441-3.
3. Harper KW, Collier PS, Dundee JW, Elliott P, Halliday NJ, Lowry KG. Age and nature of operation influence the pharmacokinetics of midazolam. *Br J Anesth* 1985;57:866-71.
4. Halliday NJ, Dundee JW, Collier PS, Loughran PG, Harper KW. Influence of plasma proteins on the onset of hypnotic action of intravenous midazolam. *Anaesthesia* 1985;40:763-6.
5. Reves JG, Newfeld P, Smith LR. Midazolam induction time: association with serum albumin. *Anesthesiology* 1981;155:A259.
6. Dundee JW, Collier PS, Carlisle RJT, Harper KW. Prolonged midazolam elimination half-life. *Br J Clin Pharmacol* 1986;21, in press.

Spinal and Epidural Anesthesia in Patients with the Acquired Immunodeficiency Syndrome

To the Editor:

Anesthesiologists generally prefer not to use epidural and subarachnoid anesthesia in patients with active or potentially progressive spinal cord lesions. An increasing number of patients with the acquired immunodeficiency syndrome (AIDS) have been found to have such disorders.

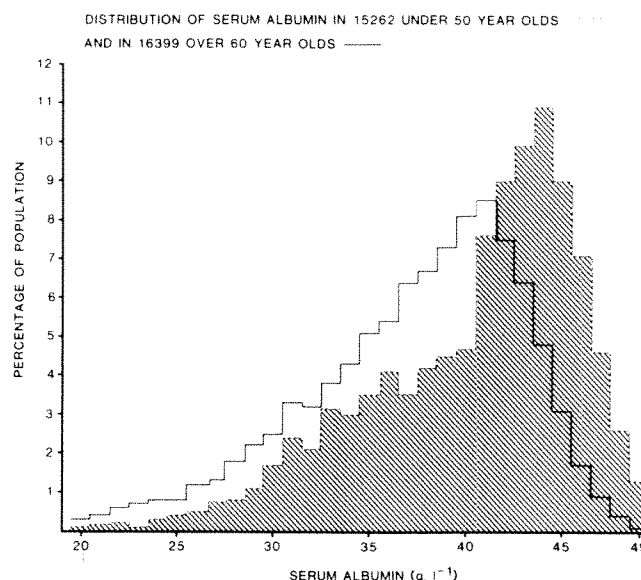


Figure 1. Distribution of serum albumin in 15,262 patients under 50 years old (---) and in 16,399 over 60 years old (—). Data obtained on routine hospital screening.

The causative agent of AIDS, the human T-lymphotropic virus type III (HTLV-III), preferentially attacks not only helper T-lymphocytes, but cells in the central nervous system (CNS) as well (1). About one fifth of the patients with AIDS develop vacuolar degeneration of the spinal cord with associated paraparesis, ataxia, and incontinence. An even greater number, about one third, develop a subacute encephalitis often leading to dementia, coma, and death (2,3). Neurologic symptoms may in fact precede the opportunistic infections and malignancies used by the Centers for Disease Control (CDC) in its definition of AIDS (3).

The virus may exist for long periods of time, it seems, in an inactive lysogenic-like state within the host cell. Certain poorly understood factors may, however, cause its conversion to an active lytic-like state (4), with rapid production of new virions and severe damage to the host cell.

In summary, there is a high prevalence of HTLV-III spinal cord infection (presumably covert as well as overt) in patients with AIDS, and the potential exists for serious flareups secondary to unknown factors in patients with inactive disease. I do not know of any reported cases in which spinal or epidural anesthesia has been thought responsible for exacerbating the neurological condition of anyone infected with HTLV-III. Still, I believe it advisable before choosing to perform such a procedure in a patient with AIDS that the anesthesiologist be aware of the frequent existence of underlying neurological pathology.

Ernest R. Greene Jr, MD, PhD
Veterans Administration Medical Center
University of Alabama at Birmingham
Birmingham, AL 35294

References

1. Black PH. HTLV-III, AIDS, and the brain. *N Engl J Med* 1985;313:1538-40.
2. Ho DD, Rota TR, Schooley RT, et al. Isolation of HTLV-III from cerebrospinal fluid and neural tissues of patients with neurologic syndromes related to the acquired immunodeficiency syndrome. *N Engl J Med* 1985;313:1493-7.
3. Holland JC, Tross S. The psychosocial and neuropsychiatric sequelae of the acquired immunodeficiency syndrome and related disorders. *Ann Intern Med* 1985;103:760-4.
4. Haase AT. The pathogenesis of slow virus infections: molecular analyses. *J Infect Dis* 1986;153:441-5.

Safety of Lacri-Lube®

To the Editor:

We recently completed experiments to see whether we could reproduce the flash fire reported by Datta (1) when Lacri-Lube® was used in the presence of cautery.

In the first of three experiments, 2.5-cm strips of Lacri-Lube ointment on a watch glass were heated directly with an Accu-Temp® Cautery (Concept, Inc.) applied at an angle of approximately 15° while exposed to nitrous oxide-oxygen (3:2) at flow rates ranging from 15.0 to 300.0 ml/min. No flash fire was observed.

In the second experiment, the same procedure was used, except that the gas was applied to the watch glass at various angles from 45 to 90° (approximately 120 and 75° to the cautery) while the cautery (at about 15° to the watch glass) was moved around the ointment. No flash fire occurred.

In the last experiment, Lacri-Lube was applied directly to a cautery tip exposed to nitrous oxide-oxygen at the flow rates mentioned above. There was no flame, but there was a small amount of smoke from the cautery tip.

We conclude from these experiments that there is no evidence of instantaneous ignition when Lacri-Lube is used in the presence of nitrous oxide-oxygen (3:2) and cautery, a conclusion supported by recently reported observations of Carpel, et al. (2).

D. Stephen Robins, MD
Allergan Pharmaceuticals, Inc.
Irvine, CA 92715

References

1. Datta TD. Flash fire hazard with eye ointment. *Anesth Analg* 1984;63:700-1.
2. Carpel EF, Rice SW, Lang M, Schochet HL. Fire risks with ophthalmic ointments. *Am J Ophthalmol* 1985;100(3):477-8.

A Regional Anesthetic Technique Compared to General Anesthesia for Outpatient Knee Arthroscopy

To the Editor:

We were most interested in the report of Patel et al. (1) of the use of the "3 in 1 block" with a separate lateral femoral

cutaneous (LFC) nerve block for knee arthroscopy. However, we were less successful than the authors when using that regional anesthetic technique. We suggest that this is due to the fact that complete anesthesia of the knee cannot be anticipated when anesthetizing the femoral, obturator, and LFC nerves. The sciatic nerve innervates the posterior aspect of the knee (2) and, depending on the reference consulted, the lateral aspect of the knee lies in the distribution of either the sciatic (3) or the LFC nerves (4).

René Martin, MD, FRCP(C)

Bruno Petit, MD

Jorge Basora, MD, FRCS(C)

Department of Anaesthesia and Orthopedic Surgery
Centre Hospitalier Universitaire de Sherbrooke
3001 12th Avenue North
Fleurimont, Quebec
J1H 5N4 Canada

References

1. Patel NJ, Flashburg MH, Paskin S, Grossman R. A regional anesthetic technique compared to general anesthesia for outpatient knee arthroscopy. *Anesth Analg* 1986;65:185-7.
2. Miller RD. *Anesthesia*, 2nd ed. New York: Churchill Livingstone, 1986:1065.
3. Cousins MJ, Bridenbaugh PO. *Neural blockade*, 1st ed. Philadelphia: J.B. Lippincott, 1980:328.
4. Moore DC. *Regional Block*, 4th ed. Springfield IL: Charles C. Thomas, 1978:286.

Transtracheal Jet Ventilation during Fiberoptic Intubation under General Anesthesia

To the Editor:

Percutaneous transtracheal jet ventilation (TJV) has been used for emergency resuscitation of patients having respiratory obstruction. The technique has been also used during anesthesia to ventilate patients undergoing microlaryngoscopy, and cases of difficult intubation (1-7). TJV can be also utilized during fiberoptic intubation in the anesthetized patient with a difficult airway.

A 17-yr-old girl with ankylosis of the temporomandibular joint secondary to fracture mandible was scheduled for bilateral subcondylar osteotomy and insertion of a silastic implant. The patient was premedicated with meperidine, 75 mg, and atropine, 0.6 mg. Before induction of anesthesia, the patient was placed in the supine position with the neck extended. Both the cricoid and thyroid cartilages were identified, and an 18-gauge needle and, through it, a plastic cannula were passed through the cricothyroid membrane into the trachea. Correct positioning was confirmed by aspiration of air through a saline-filled syringe attached to the cannula. Once the trachea was entered, the cannula was advanced while keeping the needle stationary. The needle was then removed and the cannula secured in position and connected by a high pressure tubing to oxygen that could

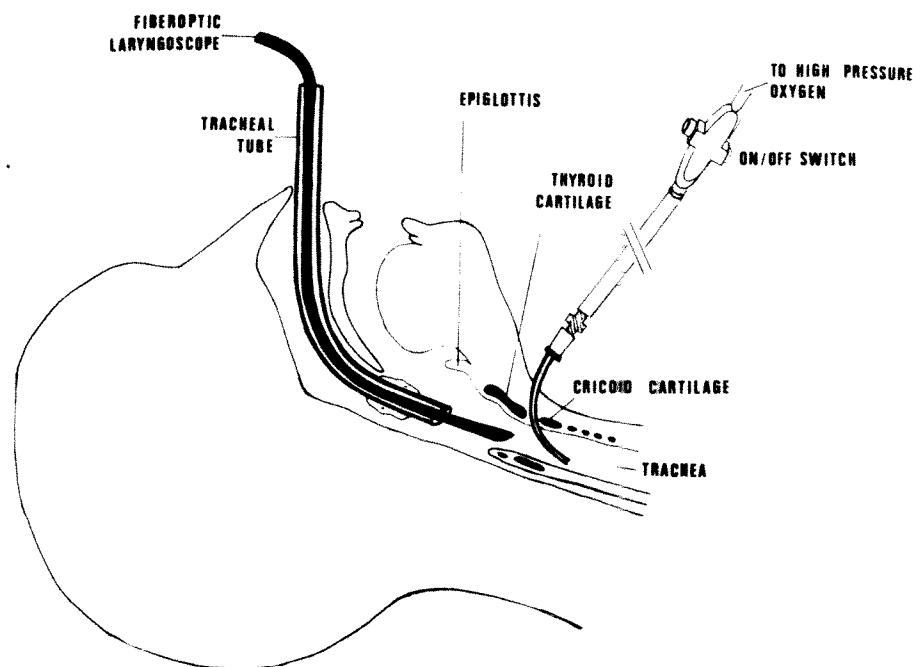


Figure 1. Schematic diagram showing nasal fiberoptic intubation while TJV is continued by a cannula inserted into the trachea via the cricothyroid membrane.

be intermittently delivered at a pressure of 60 psi. Anesthesia was then induced with thiopental, 350 mg, followed by succinylcholine, 100 mg. Intermittent transtracheal jet ventilation was then started, while the trachea was intubated via the nasal root using the fiberoptic laryngoscope (Fig. 1). After tracheal intubation, TJV was discontinued and ventilation was maintained via the tracheal tube.

Fiberoptic laryngoscopy is frequently used for tracheal intubation in patients with difficult airways. The technique is usually done in the awake patient under local analgesia (8). In anesthetized patients, ventilation and anesthesia can be delivered by a facemask with an endoscopic port (9). The endoscopic mask allows the administration of potent volatile anesthetics and a high inspired oxygen concentration, while the insertion tube of the endoscope is passed through the endoscopic port (10). As an alternative to the endoscopic mask, anesthesia and ventilation can be maintained by an oral or a binasal airway attached to the anesthesia circuit (9). Although these techniques maintain oxygenation during spontaneous breathing, they might not ensure adequate ventilation if respiration is depressed or partially obstructed in a patient with a difficult airway.

TJV bypasses the upper airways and provides an alternative technique of ventilation during fiberoptic intubation under general anesthesia. The technique permits the use of complete neuromuscular blockade and maintains uninterrupted ventilation during the procedure, while keeping the face and upper airway free for the endoscopist, and hence can provide optimal, safe, and unhurried conditions for fiberoptic tracheal intubation of the anesthetized patient with a difficult airway.

Anis Baraka, MD
Department of Anesthesiology
American University of Beirut
Beirut, Lebanon

The author is greatly indebted to Dr. Nada Usta, who drew the diagram.

References

1. Jacoby JJ, Hamelberg W, Zeigler CH, Flory FA, Jones JR. Transtracheal resuscitation. *JAMA* 1956;162:625-8.
2. Spoerel WE, Narayanan PS, Singh NP. Transtracheal ventilation. *Br J Anaesth* 1971;43:932-9.
3. Jacobs HB. Emergency percutaneous transtracheal catheter and ventilator. *J Trauma* 1972;12:50-5.
4. Klain M, Smith BR. High frequency percutaneous transtracheal jet ventilation. *Crit Care Med* 1977;5:280-7.
5. Layman PR. Bypassing a problem airway. *Anaesthesia* 1983;38:478-80.
6. Layman PR. Transtracheal jet ventilation in oral surgery. *Ann R Coll Surg Engl* 1983;65:318-20.
7. Ravussin P, Freeman J. A new transtracheal catheter for ventilation and resuscitation. *Can Anaesth Soc J* 1985;32:60-4.
8. Ovassapian A, Yalich SJ, Dykes MHM, Brunner EE. Fiberoptic nasotracheal intubation—incidence and causes of failure. *Anesth Analg* 1983;62:692-5.
9. Patil V, Stehling LC, Zauder ML, Koch JP. Mechanical aids for fiberoptic endoscopy. *Anesthesiology* 1982;57:69-70.
10. Rogers SN, Benumof JL. New and easy techniques for fiberoptic endoscopy-aided tracheal intubation. *Anesthesiology* 1983;59:569-72.

Loss of Resistance Technique for Transaortic Celiac Plexus Block

To the Editor:

We wish to report the use of a loss of resistance technique as a modification of the transaortic approach to the celiac plexus described by Ischia (1). We use this technique without radiographic assistance for diagnostic blocks but supplement it with contrast localization prior to injecting neurolytic agents.

The patient is positioned prone with a pillow under the

abdomen to flex the spine. A skin mark is made approximately 7 cm to the left of the T-12 spinous process and below the twelfth rib. The skin is aseptically prepared and draped, and a 25-gauge 1.5-in needle is utilized to infiltrate the skin and subcutaneous tissue with local anesthetic. A 20-gauge 13-cm Hink needle (Cook, Inc., Bloomington, IN) is advanced through the skin slightly cranial to the sagittal plane and about 60° to the skin surface. If the transverse process of T-12 is encountered, the needle is withdrawn and readvanced in a slightly more cranial or caudal direction to walk off the process. When the vertebral body is encountered, the needle is withdrawn slightly and redirected at a steeper angle to walk off the body. As the posterior wall of the aorta is penetrated, a pop is usually appreciated, and removal of the stylet reveals a free flow of arterial blood. A loss of resistance syringe containing 5 ml of sterile normal saline is attached to the needle, and 1 ml of blood is aspirated to ensure the absence of air bubbles. The needle is then advanced slowly, with constant pressure on the plunger of the syringe. As the needle tip enters the anterior wall of the aorta there is a sudden increase in resistance to injection followed by a loss of resistance as the needle penetrates the anterior wall and enters the retroperitoneal space. An aspiration test is performed prior to injecting agents. For di-

agnostic celiac plexus blocks 20 ml of 0.5% bupivacaine is injected. For neurolytic celiac plexus blocks, 3 ml of iohalamate meglumine (Conray 60—a water soluble intravenous contrast media) dissolved in 6 ml 0.5% bupivacaine is injected and the needle position documented by CT scan prior to injecting 20 ml of absolute alcohol.

We have performed over 100 celiac plexus blocks utilizing this technique without significant complications. The loss of resistance technique permits rapid identification of the preaortic retroperitoneal space without the need for radiographic assistance. Prior to injecting neurolytic agents we utilize a CT scan to document proper needle position as well as appropriate spread of contrast solution.

Gary S. Feldstein, MD

Steven D. Waldman, MD

Mark L. Allen, MD

*Pain Consortium of Kansas City
Kansas City, MO 64114*

Reference

1. Ischia S, Luzzani A, Ischia A, Faggion S. A new approach to the neurolytic block of the coeliac plexus: the transaortic technique. *Pain* 1983;16:333-41.

Book Reviews

Anesthesia and Sedation in the Dental Office

Raymond A. Dionne and Daniel M. Laskin, eds. NY: Elsevier Science Publishing Company, Inc., 1986, 170 pp, \$65.00.

This text represents the edited presentation of a consensus conference held at and sponsored by the National Institutes of Health. It was the intention of the individuals organizing this event to bring together established experts in the field of anesthesia and sedation in the dental setting to delineate the state of the art in this area. The editors of this compilation suggest that it would be appropriate for those individuals interested in getting an introduction to the status of anesthesia and sedation techniques in dentistry. This reviewer agrees with this assessment. Between two and five million procedures classifiable as sedation and/or anesthesia are performed yearly in dental offices. It is appropriate that this huge mass of experience come to the attention of the specialist in anesthesia.

The quality of the individual efforts of this multiauthored text is uniformly high. The presentations are generally erudite, well-written, concise, and to the point. The text is less of a cookbook than a logical presentation of technique with emphasis on explanatory rather than rote material.

The difficulties that I have with the book are relatively minor. They have to do with the fact that the internal vocabulary, as often occurs in multiauthored volumes, is not necessarily consistent from monograph to monograph. This is because the editors took pains to allow the various authors their own voice; multiple generations of practitioners are represented and various regional (geographic) techniques are discussed.

The final chapter is a consensus statement and reviews the entire area of anesthesia and sedation in the dental setting. It is a well-thought-out presentation of the state of the art. It makes a subdued plea for the appropriate training of individuals with primary dental orientation to take at least one year of advanced training in anesthesia in a hospital setting so as to bring dentistry the benefits available from teaching programs in anesthesia. This reviewer concurs with this objective and recommends this book for anyone interested in the field of outpatient sedation in general or the application of these techniques to dentistry in particular.

Sanford L. Klein, DDS, MD
Professor and Chairman, Department of Anesthesia
Robert Wood Johnson Medical School
New Brunswick, NJ 08903

Cardiac Catheterization and Angiography (3rd ed.)

William Grossman, ed. Philadelphia: Lea & Febiger, 1986, 562 pp, \$49.50.

Historically, this text has served as the most authoritative book on the principles and techniques of cardiac catheterization. The third edition continues this excellent tradition and represents a lifetime of interest and study by the editor. In this text Dr. Grossman, together with 22 contributing authors, all recognized experts in the field of cardiology, provide the scientific foundations and the clinical knowledge that are fundamental to cardiac catheterization.

In general, the text is well-organized, covering all aspects of cardiac catheterization and angiography, with a clear and concise description of the major techniques currently employed. A distinctive hallmark of this text is the integration of physiologic principles with catheterization and angiographic techniques.

The book begins with a section on general principles of cardiac catheterization and angiography, emphasizing the physiologic and technical features that impact on cardiac catheterization. The second section of the text deals with techniques of catheter placement. It includes detailed discussions of percutaneous catheterization, balloon-tip flow-directed catheters, and special considerations in catheterization of infants and children. The third section, "Evaluation of Cardiac Function," is unique and refreshing. It addresses the current state of the art in the evaluation of systolic and diastolic ventricular function, myocardial blood flow, dynamic and isometric exercise, and electrophysiologic techniques.

The section on "Special Catheter Techniques" has been greatly expanded since the second edition and now contains chapters on coronary angiography, application of lasers, and coronary angiography in the cardiac catheterization lab. These chapters reflect the growth and the exciting developments in invasive cardiology in recent years. The final section provides a discussion of the interpretation of hemodynamic and angiographic findings in specific disorders. In this last section, the clinical expertise and management strategy of the authors is highlighted in their interpretation of catheterization data.

This excellent text is not for the generalist. It contains highly specialized material and is aimed at the instruction of physicians who deal intensively with cardiovascular patients. This text is especially recommended for those physicians whose clinical practice of medicine depends heavily

upon the interpretation and assessment of cardiac catheterization data.

In the preface, Dr. Grossman states "I hope that this book will be of value not only to those involved in the daily practice of cardiac catheterization and angiography, but to all those who are involved in the care of patients with serious heart disease." I believe this text admirably accomplishes this intention. Clinicians involved in the care of patients with cardiovascular disease will find this text an invaluable resource and supplement to other major texts.

William J. Greeley, MD
Assistant Professor of Anesthesiology and Pediatrics
Duke University Medical Center
Durham, NC 27710

Muscle Relaxants: Basic and Clinical Aspects

Ronald L. Katz, ed. Orlando, FL: Grune and Stratton, 1985, 305 pp, \$24.50.

In many ways, this text is an update of Dr. Katz's previous book on the same subject. This material was initially presented as the December 1984 (Vol. 3, No. 4) and March 1985 (Vol. 4, No. 1) issues of the journal *Seminars in Anesthesia*.

The book is a multiauthored text by experts in the field. It is not designed to be an encyclopedic reference concerning either the physiology of neuromuscular transmission or the actions of muscle relaxants and, as a result, those who do research in the area of neuromuscular transmission will find little new in this text. For the resident and practicing clinician, however, this book is a well-balanced volume concerning both the basic and clinical aspects of actions of neuromuscular blocking drugs.

The book begins with three commendable chapters. In the first, Dr. F.J. Standaert presents the current concepts of the architecture of the cholinergic receptor and the mechanisms by which acetylcholine and blocking drugs interact with both the receptor and the ionic channels. The second chapter, by Dr. N.N. Durant, describes the processes involved with the synthesis, storage, mobilization, and release of acetylcholine from the nerve terminal, as well as its action with the postsynaptic cholinergic receptor. The third chapter contains a controversial concept. The authors, W.C. Bowman, I.G. Marshall, and A.J. Gibb, state at the beginning their belief in the concept that receptors for acetylcholine exist on the nerve terminal and that the function of these receptors is to regulate the output of acetylcholine resulting from nerve stimulation. This is an important concept, and the authors properly devote much time elucidating and supporting their belief in it. They also present a very cogent argument that tetanic fade seen with *d*-tubocurarine and other nondepolarizing neuromuscular blocking drugs is a result of the action of these drugs on the presynaptic cholinergic receptors.

The succeeding chapters by and large maintain the high quality set by the introductory material. Where controver-

sial statements are made, the editor has been careful to make note of them. The chapter on succinylcholine by C. Lee presents an interesting overview of this rather controversial drug, while those on atracurium and vecuronium by Drs. J.T. Payne and R.D. Miller, respectively, present the clinical pharmacology of these newly introduced agents.

The chapter by H. Rosenberg ("Neuromuscular Blockade in Patients with Neuromuscular Disorders") is noteworthy for providing a concise compendium of current knowledge of the interaction between these rather rare diseases and neuromuscular blocking agents. The pharmacokinetics and pharmacodynamics of reversal of neuromuscular blockade are described well by Dr. Cronnelly.

One of the most interesting chapters is that by J. Viby-Mogensen on the interaction of other drugs with muscle relaxants. This is a very complex subject, and Dr. Viby-Mogensen has wisely chosen to handle it by presenting the various drugs in their interactions in a tabular form. He includes both the interacting drug, its proposed mechanism of action, and the clinical effects of this interaction along with appropriate comments.

In summary, though this book does not completely cover the pharmacology of neuromuscular blocking drugs, its breadth of coverage combined with its clinical applicability make it a worthwhile addition to the library of the resident in training or the practicing clinician. It will add little to the individual with specialized interests in neuromuscular physiology and pharmacology.

Martin D. Sokoll, MD
Professor of Anesthesia
University of Iowa School of Medicine
Iowa City, IA 52242

Head Injury and the Anaesthetist

W. Fitch and J. Barker, eds. Amsterdam: Elsevier Science Publishers, BV, 1985, 278 pp, \$81.50.

Books should be judged against the intentions of the authors and/or editors. This caveat clearly applies to this text. Many readers might carelessly purchase such a book hoping it to be a comprehensive review of "how to anesthetize the patient with a head injury." It most decidedly is not. In the words of the editors, "anyone looking for a recipe on how to treat the head-injured patient will be disappointed." Instead, it is an attempt to bring together the views of a variety of experts (neuropathologists, neurosurgeons, physiologists, and anesthesiologists) into a single source that can serve as a reference for individuals with an interest in head injury and anesthesia. The text is a multiauthored work divided into 14 chapters. It begins with a detailed discussion of gross and microscopic pathology, followed in turn by chapters on pathophysiology (which focus on the problem of secondary injury), pulmonary function, and clinical assessment (which is heavily oriented toward "quantitative" scales, e.g., the Glasgow coma score and similar materials).

These form the "background" material, which are then supplemented by more clinically oriented chapters on immediate care and transport, anesthesia (the only chapter in the book that deals directly with anesthesia), postoperative care, artificial ventilation, ICP monitoring (which is too brief), facial injuries and associated chest trauma, barbiturate therapy, and brain death. Most of these are excellent, or at worst, adequate but mundane surveys of their respective subjects. There is a great deal of redundancy in the area of respiratory care. Each of the six(!) chapters that deal with some aspect of this subject contains useful and unique information, but some consolidation would have been welcome. On a positive note, however, are the chapters by Dr. Sheila Jennett (on basic pulmonary pathophysiology), and by the late Dr. Gordon McDowall (to whom the book is dedicated), which deal with artificial ventilation. The former is perhaps the best chapter in the book and one of the best I've read on this subject, while Professor McDowall intelligently and critically analyzes the "sacred cow" of prolonged controlled hyperventilation. Due to editorial delays, at least one chapter—the one dealing with barbiturate therapy—is a bit out of date, and more recent outcome trials are not discussed (although noted in an appendix). It does, however, serve as an excellent review by authors who have been intimately involved in the area since its inception (Drs. Harvey Shapiro and Larry Marshall).

In summary, this is a very good book. Residents and some practitioners may reasonably decide against its purchase. This does not mean that the book has little to offer practicing anesthesiologists, but it may be the wrong one for people whose time is limited, and who deal with such clinical situations only infrequently. By contrast, for those who spend the bulk of their time practicing neuroanesthesia or neurosurgical intensive care—or the academic versions of these disciplines—the book may prove to be indispensable. It definitely belongs in every departmental library (anesthesia and neurosurgical), and in the collections of physicians (anesthesiologists, intensivists, neurosurgeons, and perhaps even some neurologists) with a serious clinical or research interest in head trauma.

Michael M. Todd, MD
Department of Anesthesia
University of Iowa School of Medicine
Iowa City, IA 52242

Matters of Life and Death: Risks vs Benefits of Medical Care

Eugene D. Robin. Stanford, CA: The Portable Stanford, 1984, 205 pp, \$9.95.

This is a brief and very readable treatise, which the author claims is written for patients. The author is a well-known

medical scholar, and I suspect knows that the greatest impact of this book really will be the message it delivers to physicians. No doubt, however, patients and prospective patients will benefit from this book as well. The physician reader may be offended by this book, as it challenges (purposefully) much of what we do. Careful and complete reading, however, will substantiate the challenge raised.

Examples are provided to expand our concepts of risk, benefit analysis, iatrogenic harm, the very complicated ways we have developed to care for the critically ill, wholesale screening of patients, the care of the aged, and the changing position of the doctor on his or her pedestal. It is quite likely that if this material could be thoroughly ingrained in medical students, we would be producing improved deliverers of health care from our medical schools. Of particular importance is the repetitive message that we have not and do not base much of our advice to patients on the basis of good clinical trials.

The book does an excellent job of fulfilling its designated rationale, namely, that there are serious flaws in basic processes by which diagnostic and therapeutic measures are introduced in medicine and that many of these flaws can be changed. The final chapter of the book is a brief statement of recommendations for change.

The specialty of Anesthesia is only casually mentioned in this book, but all principles discussed apply. In fact, they may be more applicable to us, since our ministrations are rarely therapeutic in nature. The risks should therefore be very carefully scrutinized. It is difficult to believe that things that seem so logical and so correct can, in fact, be lacking in benefit and even productive of harm to patients we endeavor to help. All of us would benefit by reading this book carefully and thoughtfully.

William K. Hamilton, MD
Professor of Anesthesia
Associate Dean, School of Medicine
University of California San Francisco
San Francisco, CA 94143

Books Received

Receipt of the following books from their publishers is acknowledged with thanks. Selected books from this list will be reviewed in the future.

Altura BM, Halevy S, eds. Cardiovascular Actions of Anesthetics and Drugs Used in Anesthesia. Volume 1, Basic Aspects. Basel: S Karger AG, 1986, 268 pp, \$108.50.

Hatch DJ, Sumner E. Neonatal Anaesthesia and Perioperative Care, 2nd Edition. Volume 5, Current Topics in Anaesthesia Series. Baltimore: Edward Arnold, 1986, 271 pp, \$59.50.

Kofke WA, Levy JH. Postoperative Critical Care Procedures of the Massachusetts General Hospital. Boston: Little Brown Co., 1986, 544 pp, \$18.50.

Paganini EP, ed. Acute Continuous Renal Replacement Therapy. Boston: Martina Nijhoff Publishing, 1986, 292 pp, \$42.50.

Stoelting RK, Barash PG, Gallagher TJ. Advances in Anesthesia, Volume 3. Chicago: Year Book Medical Publishers, 1986, 403 pp, \$55.95.

A Guide for Authors

Manuscripts should be sent to:

Nicholas M. Greene, MD

Editor in Chief

Anesthesia and Analgesia

Yale University School of Medicine

333 Cedar Street, New Haven, CT 06510

Editorial Policies

Anesthesia and Analgesia, the oldest publication for the specialty of anesthesiology, is the official voice of the International Anesthesia Research Society. It publishes original articles, clinical reports, technical communications, review articles, and letters to the editor.

All papers are reviewed by three or more referees. Acceptance is based upon significance, originality, and validity of the material presented. Only one copy of the articles not accepted for publication will be returned to the author.

The submitted manuscript should be accompanied by a covering letter that must include a statement to the editor about all submissions and previous reports that might be regarded as prior or duplicate publication of the same, or very similar, work. The title page and abstract of such material should be included with the submitted manuscript to help the editor decide how to deal with the matter.

Manuscripts must be prepared and submitted in the manner described in "Uniform Requirements for Manuscripts Submitted to Biomedical Journals," reprinted in *Annals of Internal Medicine* 1982;96:766-71 and *Lancet* 1982;284:1766-70.

No manuscripts describing investigations carried out in humans will be accepted for publication unless the text states that the study was approved by the authors' institutional human investigation committee and that written informed consent was obtained from all subjects or, in minors, by parents. No manuscript describing investigations in animals will be accepted for publication unless the text states that the study was approved by the authors' institutional animal investigation committee.

Human subjects should not be identifiable. Do not use patients' names, initials, or hospital numbers.

Authors and their typists should use the checklist given below for preparation of manuscripts:

General

- ☐ Original articles describe in 3000 words or less clinical or laboratory investigations.
- ☐ Clinical reports describe in 1000 words or less either new and instructive case reports or anesthetic techniques and equipment of demonstrable originality, usefulness, and safety.
- ☐ Technical communications are papers that deal with instrumentation and analytic techniques.
- ☐ Review articles of 2500 to 4000 words collate, describe, and evaluate previously published material to aid in evaluating new concepts.
- ☐ Letters to the editor, less than 300 words in length, include brief constructive comments concerning previously published articles or brief notations of general interest. The manuscripts must be double spaced, and a title and three copies must be provided.
- ☐ Type manuscripts on white bond paper, 216 by 279 mm (8½ by 11 in.) or ISO A4 (212 by 297 mm) with margins or at least 25 mm (1 in) using double spacing throughout.
- ☐ Begin each of the following sections on separate pages: title page, abstract and key words, text, acknowledgments, references, tables (each table, complete with title and footnotes, should be on a separate page), and legends. Type only on one side of the paper and number pages consecutively, beginning with the title page. Type the page number in the upper right-hand corner of each page.
- ☐ Submit three copies of manuscript and figures in a heavy paper envelope. Submitted manuscripts should be accompanied by a covering letter, and permissions to reproduce previously published materials or to use illustrations that may identify subjects.
- ☐ Authors should keep copies of everything submitted.

Title Page

- ☐ The title page should contain the title of the article, which should be concise but informative;
- ☐ A short running head or footline of no more than 40 characters (count letters and spaces) placed at the foot of the title page and identified;
- ☐ First name, middle initial, and last name of each author, with highest academic degree(s);
- ☐ Name of department(s) and institution(s) to which the work should be attributed;
- ☐ Disclaimers, if applicable;
- ☐ Name and address of author responsible for correspondence about the manuscript.
- ☐ Name and address of author to whom requests for reprints should be addressed, or a statement that reprints will not be available from the author;
- ☐ The source(s) of support in the form of grants.

Abstract and Key Words

- ☐ The second page should carry an abstract of not more than 150 words. (Abstracts are not needed for Clinical Reports.)
- ☐ The abstract should state the purposes of the study or investigation, basic procedures (study subjects or experimental animals; observational and analytic methods), main findings (give specific data and their statistical significance, if possible), and the principal conclusions. Emphasize new and important aspects of the study or observations.
- ☐ Define all abbreviations except those approved by the International System of Units.
- ☐ Key (indexing) terms: Below the abstract, provide (and identify as such) 3 to 10 key words or short phrases that will assist indexers in cross indexing the article and that may be published with the abstract.

Text

- ☐ The text of observational and experimental articles is usually—but not necessarily—divided into sections with the headings Introduction, Methods, Results, and Discussion.
- ☐ Case reports, reviews, and editorials do not require the above sections.
- ☐ **Introduction:** Clearly state the purpose of the article. Summarize the rationale for the study or observation. Give only strictly pertinent references, and do not review the subject extensively.
- ☐ **Methods:** Describe the selection of observational or experimental subjects (patients or experimental animals, including controls) clearly. Identify the methods, apparatus (manufacturer's name and address in parentheses), and procedures in sufficient detail to allow other workers to reproduce the results. Give references to established methods, including statistical methods; provide references and brief descriptions for methods that have been published but are not well known; describe new or substantially modified methods, give reasons for using them, and evaluate their limitations.
- ☐ Identify precisely all drugs and chemicals used, including generic name(s), dosage(s), and route(s) of administration.

- ☐ **Results:** Present the results in logical sequence in the text, tables, and illustrations. Do not repeat in the text all the data in the tables and/or illustrations; emphasize or summarize only important observations.
- ☐ **Discussion:** Emphasize the new and important aspects of the study and conclusions that follow from them. Do not repeat in detail data given in the Results section. Include in the Discussion the implications of the findings and their limitations and relate the observations to other relevant studies. Link the conclusions with goals of the study but avoid unqualified statements and conclusions not completely supported by the data.
- ☐ **Units of measurement:** Measurements of distance/length and weight must be expressed in metric units only. Clinical laboratory and hematologic data must be expressed in **SI units** with, if desired, present conventional metric units in parentheses.

References

All references must be available to all readers. Cite only references to books and articles or abstracts published in peer reviewed Index Medicus journals. Abstracts appearing only in programs of meeting are not acceptable, nor are abstracts more than five years old.

- ☐ Number references consecutively in the order in which they are first mentioned in the text, except in review articles when references may be arranged alphabetically.
- ☐ Identify references in text, tables, and legends by arabic numbers (in parentheses, on line)
- ☐ Use the style of the examples below, which are based on the format used by the US National Library of Medicine in *Index Medicus*.
- ☐ The titles of journals must be abbreviated according to the style used in *Index Medicus*.
- ☐ References must be verified by the author(s) against the original documents.
- ☐ Examples of correct forms of references are given below:

Journals:

1. *Standard Journal Articles* (List all the authors when six or less; when seven or more, list only the first three and add et al.)
You CH, Lee KY, Chey RY, Menguy R. Electrogastrographic study of patients with unexplained nausea, bloating and vomiting. *Gastroenterology* 1980;79:311-4
2. *Personal author(s) books and monographs*
Eisen HN. Immunology: an introduction to molecular and cellular principles of the immune response. 5th ed. New York: Harper and Row, 1974:406.
3. *Chapter in a book*
Weinstein L, Swartz, NM. Pathogenic properties of invading microorganisms. In: Sodeman WA, Jr, Sodeman WA, eds. Pathologic physiology: mechanisms of disease. Philadelphia: WB Saunders, 1974:457-72.

Tables

- ☐ Type each table double spaced on a separate sheet. Do not submit tables as photographs.
- ☐ Number tables consecutively and supply a brief title for each. Give each column a short or abbreviated heading.
- ☐ Place explanatory matter in footnotes, not in the heading. Explain in footnotes all nonstandard abbreviations that are used

in each table. For footnotes, use lowercase italicized letters in alphabetical order.

- ☐ Do not use internal horizontal or vertical rules.
- ☐ Cite each table in the text in consecutive order.
- ☐ If data are used from another published or unpublished source, obtain permission and acknowledge fully.

Illustrations

- ☐ Submit three complete sets of figures. Figures should be in black and white only and professionally drawn and photographed; freehand or typewritten lettering is unacceptable. Note: Art work of published articles will not be returned.
- ☐ Instead of original drawings, roentgenograms, or other material send sharp, unmounted, glossy black-and-white photographic prints, usually 127 by 173 mm but no larger than 203 by 254 mm.
- ☐ Each figure must have a label pasted on its back indicating the number of the figure, the names of the authors, and the top of the figure. Do not write on the back of the figures or mount them on cardboard, or scratch or mar them by using paper clips. Do not bend figures.
- ☐ Photomicrographs must have internal scale markers. Symbols, arrows, or letters used in the photomicrographs should contrast with the background.
- ☐ Cite each figure in the text in consecutive order. If a figure has been published, acknowledge the original source and submit written permission from the copyright holder to reproduce the material. Permission is required, regardless of authorship or publisher, except for documents in the public domain.

Legends for Illustration

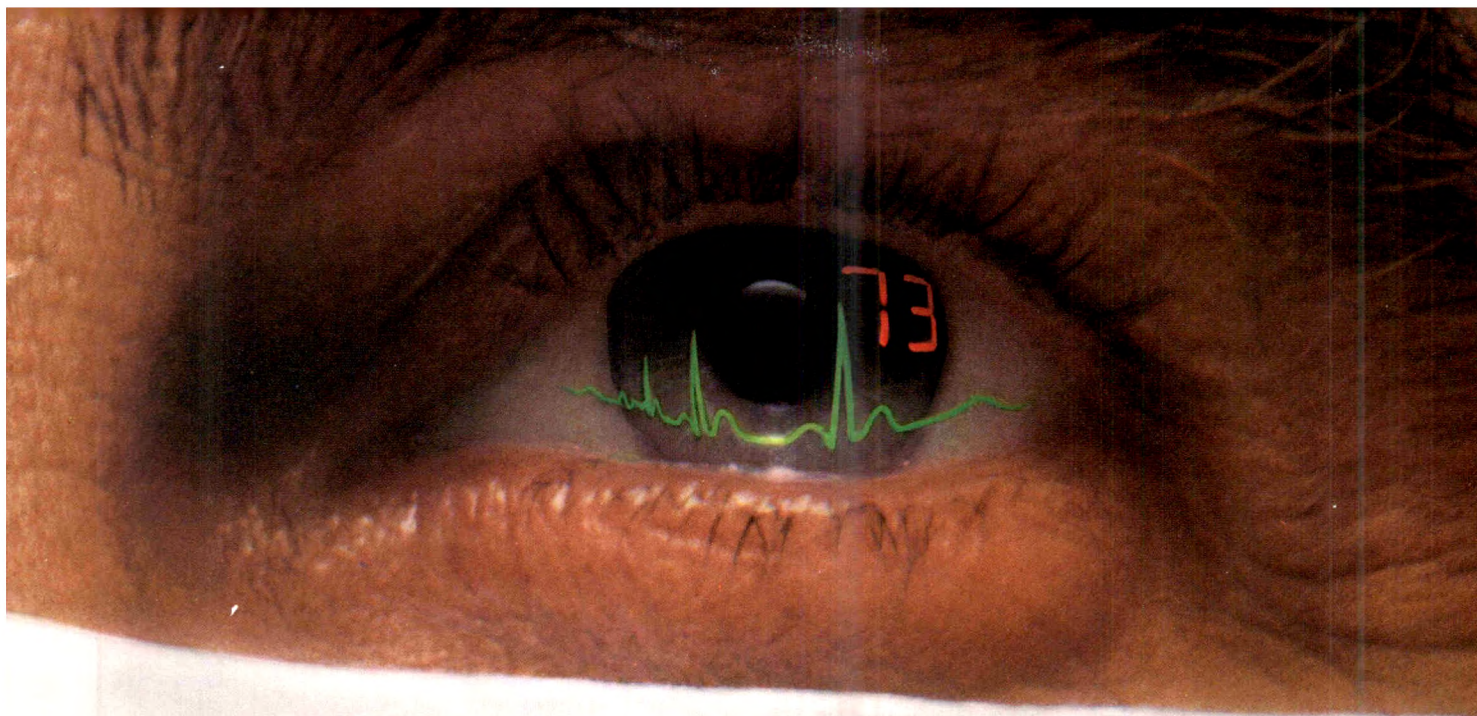
- ☐ Type legends for illustrations double spaced starting on a separate page, with arabic numerals corresponding to the illustrations.
- ☐ When symbols, arrows, numbers, or letters are used to identify parts of the illustrations, identify and explain each one clearly in the legend.

Abbreviations

- ☐ The full term for which an abbreviation stands should precede its first use in the text unless it is a standard unit of measurement. Avoid abbreviations in the title.
- ☐ Do not synthesize new or unusual abbreviations. When many abbreviations are used, include all in a box of definitions at the start of the article.
- ☐ Consult the following sources for abbreviations:
 1. CBE Style Manual Committee. Council of Biology Editors style manual: a guide for authors, editors, and publishers in the biological sciences. 4th ed. Arlington, Virginia: Council of Biology Editors, 1978; and
 2. O'Connor M, Woodford FP. Writing scientific papers in English: an ELSE-Ciba Foundation guide for authors. Amsterdam: Elsevier-Excerpta Medica, 1975.

Exclusive Publication Statement

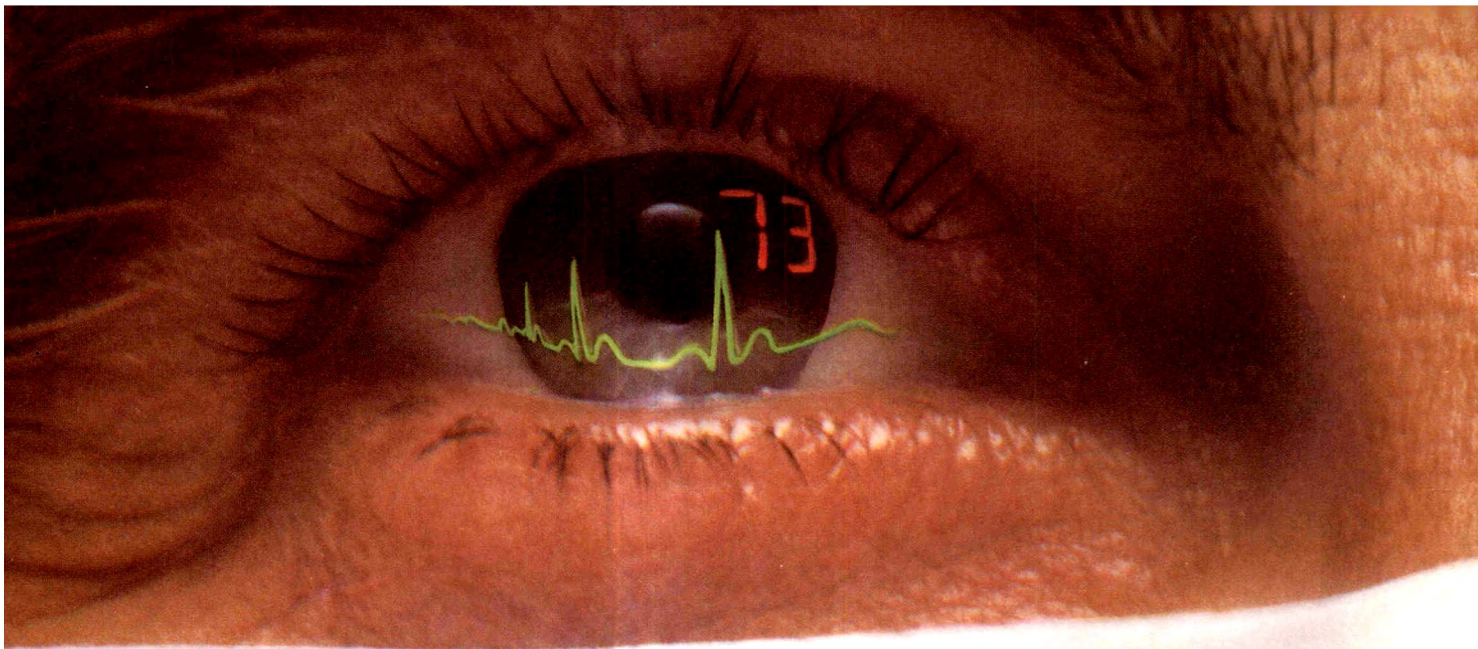
- ☐ The principal author of all materials submitted for publication (except letters to the editor) must include in a covering letter a statement to the effect that none of the material in this manuscript has been published previously nor is any of this material currently under consideration for publication elsewhere.
- ☐ Authors will be asked to transfer copyright of articles accepted for publication to the International Anesthesia Research Society.



See for yourself.

**The only surgical muscle relaxant
free of clinically significant
cardiovascular and histamine-
related side effects...**

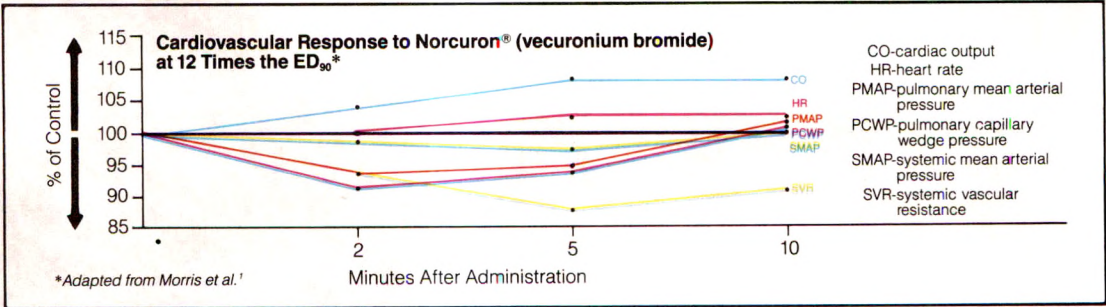
**ideal for your patients, including
those at risk.¹⁻⁵**



See the safety for yourself.

Free of clinically significant cardiovascular effects.*

NORCURON® is the only surgical muscle relaxant for which no clinically significant cardiovascular effects were observed in clinical trials.¹⁻⁴ In fact, even at 12 times effective doses, under halothane anesthesia,¹ NORCURON® produced no tachycardia, hypotension, or abnormalities of cardiodynamic function.

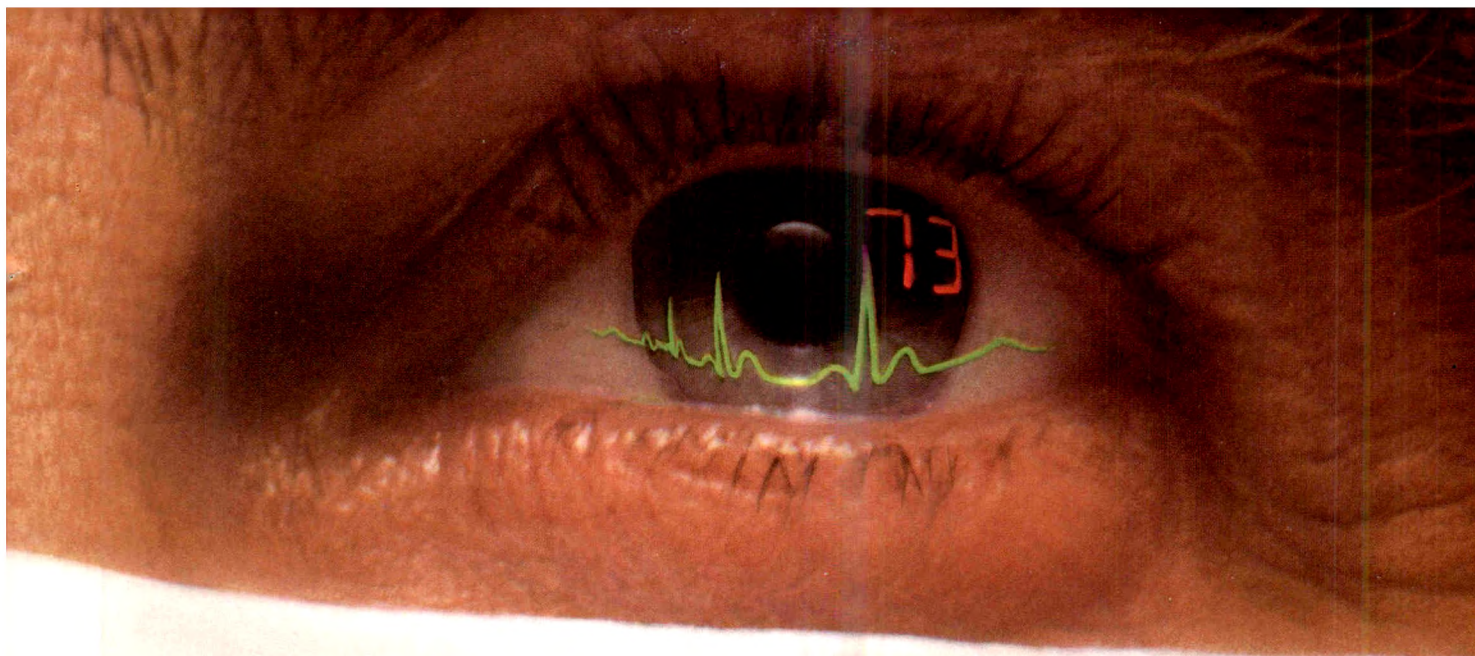


Histamine release or histamine-related side effects unlikely to occur...even at 3.5 times the ED₉₅.⁵

NORCURON® has not been shown to significantly affect circulating histamine, mean arterial blood pressure, and heart rate even in doses at the upper extreme of the recommended clinical range.⁵

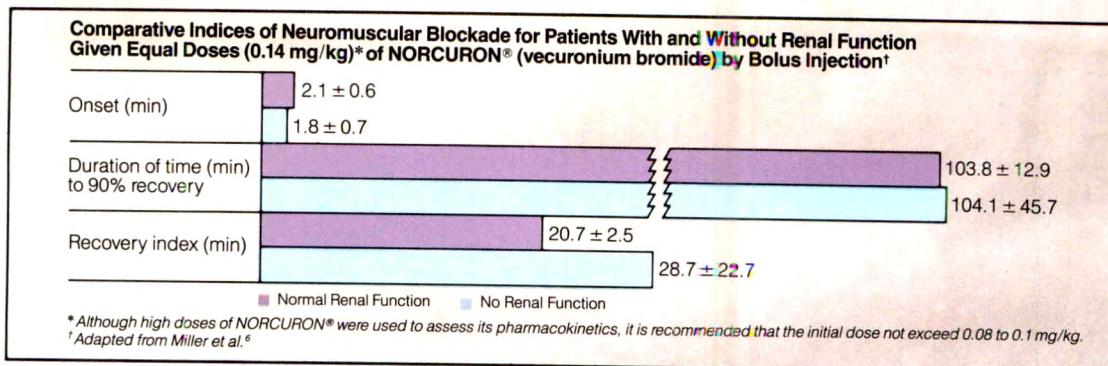
The Effect of Nondepolarizing Muscle Relaxants*				Percent of Control		
Drug	Dose (mg/kg)	xED ₉₅	Histamine	Mean Arterial Pressure	Heart Rate	
Tubocurarine	0.5	1	410	78	116	
Metocurine	0.5†	2	212	79	119	
Atracurium	0.6†	3	192	80	108	
Vecuronium	0.1	1.7	117	100	99	
Vecuronium	0.2	3.5	87	99	102	

*Adapted from Basta et al.⁵
†0.1 mg/kg higher than recommended dose.



Performance unaffected by renal function.⁶

Despite administration of high doses of NORCURON®, no significant differences in onset time, duration of action, or recovery index have been noted between patients with and without renal function.⁶



**The surgical muscle relaxant
ideal for virtually all patients
including those at risk.**

Norcuron®

(vecuronium bromide) injection

See full prescribing information on following page.

References: 1. Morris RB, et al: The cardiovascular effects of vecuronium (ORG NC 45) and pancuronium in patients undergoing coronary artery bypass grafting. *Anesthesiology* 1983; 58:438-440. 2. Durant NN: Norcuron®—a new nondepolarizing neuromuscular blocking agent. *Semin Anesth* 1982; 1:47-56. 3. Krieg N, Crul JF, Booi LH: Relative potency of ORG NC 45, pancuronium, alcuronium, and tubocurarine in anesthetized man. *Br J Anaesth* 1980; 52:783-787. 4. Gallo JA, et al: Hemodynamic effects of bolus injection of

vecuronium in cardiac surgical patients. *Anesthesiology* 1984; 61:A63. 5. Basta SJ, et al: Vecuronium does not alter serum histamine within the clinical dose range. *Anesthesiology* 1983; 59:A273. 6. Miller RD, et al: Pharmacokinetics of vecuronium in patients with kidney disease, in Agoston S, et al (eds): *Clinical Experiences with Norcuron* (ORG NC 45, Vecuronium Bromide). Amsterdam, Excerpta Medica, 1983, p 124.

Norcuron® (vecuronium bromide) injection

THIS DRUG SHOULD BE ADMINISTERED BY ADEQUATELY TRAINED INDIVIDUALS FAMILIAR WITH ITS ACTIONS, CHARACTERISTICS, AND HAZARDS.

DESCRIPTION: NORCURON® (vecuronium bromide) injection is a nondepolarizing neuromuscular blocking agent of intermediate duration, chemically designated as piperidinium, 1-(29, 30, 5a, 16b, 17b)-3, 17-bis(acetoxy)-2-(1-piperidinyl)endro-16-yl-1-methyl-, bromide.

Norcuron® is supplied as a sterile nonpyrogenic freeze-dried buffered cake of very fine microscopic crystalline particles for intravenous injection only. Following reconstitution with solvent (water for injection) the resultant solution is isotonic and has a pH of 4. Each 5 ml vial contains 10 mg vecuronium bromide. Each vial also contains citric acid, dibasic sodium phosphate, sodium hydroxide, and/or phosphoric acid to buffer and adjust pH and mannitol to make isotonic.

CLINICAL PHARMACOLOGY: Norcuron® (vecuronium bromide) injection is a nondepolarizing neuromuscular blocking agent possessing all of the characteristic pharmacological actions of this class of drugs (curariform). It acts by competing for cholinergic receptors at the motor end-plate. The antagonism to acetylcholine is inhibited and neuromuscular block is reversed by acetylcholinesterase inhibitors such as neostigmine, edrophonium, and pyridostigmine. Norcuron® is about 1/3 more potent than pancuronium; the duration of neuromuscular blockade produced by Norcuron® is shorter than that of pancuronium at initially equipotent doses. The time to onset of paralysis decreases and the duration of maximum effect increases with increasing Norcuron® doses. The use of a peripheral nerve stimulator is of benefit in assessing the degree of muscular relaxation.

The ED₅₀ (dose required to produce 50% suppression of the muscle twitch response with balanced anesthesia) has averaged 0.057 mg/kg (0.049 to 0.062 mg/kg in various studies). An initial Norcuron® dose of 0.08 to 0.10 mg/kg generally produces first depression of twitch in approximately 1 minute, good or excellent intubation conditions within 2.5 to 3.0 minutes, and maximum neuromuscular blockade within 3 to 5 minutes of injection in most patients. Under balanced anesthesia, the time to recovery to 25% of control (clinical duration) is approximately 25 to 40 minutes after injection and recovery is usually 95% complete approximately 45-65 minutes after injection of intubating dose. The neuromuscular blocking action of Norcuron® is slightly enhanced in the presence of potent inhalational anesthetics. If Norcuron® is first administered more than 5 minutes after the start of the inhalation of enflurane, isoflurane, or halothane, or when steady state has been achieved, the intubating dose of Norcuron® may be decreased by approximately 15% (see DOSAGE AND ADMINISTRATION section). Prior administration of succinylcholine may enhance the neuromuscular blocking effect of Norcuron® and its duration of action. With succinylcholine as the intubating agent, initial doses of 0.04-0.06 mg/kg of Norcuron® will produce complete neuromuscular block with clinical duration of action of 25-30 minutes. If succinylcholine is used prior to Norcuron®, the administration of Norcuron® should be delayed until the patient starts recovering from succinylcholine-induced neuromuscular blockade. The effect of prior use of other nondepolarizing neuromuscular blocking agents on the activity of Norcuron® has not been studied (see Drug Interactions).

Repeated administration of maintenance doses of Norcuron® has little or no cumulative effect on the duration of neuromuscular blockade. Therefore, repeat doses can be administered at relatively regular intervals with predictable results. After an initial dose of 0.08 to 0.10 mg/kg under balanced anesthesia, the first maintenance dose (suggested maintenance dose is 0.010 to 0.015 mg/kg) is generally required within 25 to 40 minutes; subsequent maintenance doses, if required, may be administered at approximately 12 to 15 minute intervals. Halothane anesthesia increases the clinical duration of the maintenance dose only slightly. Under enflurane a maintenance dose of 0.010 mg/kg is approximately equal to 0.015 mg/kg dose under balanced anesthesia.

The recovery index (time from 25% to 75% recovery) is approximately 15-25 minutes under balanced or halothane anesthesia. When recovery from Norcuron® neuromuscular blocking effect begins, it proceeds more rapidly than recovery from pancuronium. Once spontaneous recovery has started, the neuromuscular block produced by Norcuron® is readily reversed with various anticholinesterase agents, e.g., pyridostigmine, neostigmine, or edrophonium in conjunction with an anticholinergic agent such as atropine or glycopyrrolate. There have been no reports of recurarization following satisfactory reversal of Norcuron® induced neuromuscular blockade; rapid recovery is a finding consistent with its short elimination half-life.

Pharmacokinetics: At clinical doses of 0.04-0.10 mg/kg, 60-80% of Norcuron® is usually bound to plasma protein. The distribution half-life following a single intravenous dose (range 0.025-0.280 mg/kg) is approximately 4 minutes. Elimination half-life over this same dosage range is approximately 65-75 minutes in healthy surgical patients and in renal failure patients undergoing transplant surgery. In late pregnancy elimination half-life may be shortened to approximately 35-40 minutes. The volume of distribution at steady state is approximately 300-400 ml/kg; systemic rate of clearance is approximately 3-4.5 ml/minute/kg. In man, urine recovery of Norcuron® varies from 3-35% within 24 hours. Data derived from patients requiring insertion of a T-tube in the common bile duct suggests that 25-50% of a total intravenous dose of vecuronium may be excreted in bile within 42 hours. Only unchanged Norcuron® (vecuronium bromide) injection has been detected in human plasma following clinical use. One metabolite, 3-deacetyl vecuronium, has been recovered in the urine of some patients in quantities that account for up to 10% of injected dose; 3-deacetyl vecuronium has also been recovered by T-tube in some patients accounting for up to 25% of the injected dose.

This metabolite has been judged by animal screening (dogs and cats) to have 50% or more of the potency of Norcuron®, equipotent doses are of approximately the same duration as Norcuron® in dogs and cats. Biliary excretion accounts for about half the dose of Norcuron® within 7 hours in the anesthetized rat. Circulatory bypass of the liver (cat preparation) prolongs recovery from Norcuron®. Limited data derived from patients with cirrhosis or cholestasis suggests that some measurements of recovery may be doubled in such patients. In patients with renal failure, measurements of recovery do not differ significantly from similar measurements in healthy patients.

Studies involving routine hemodynamic monitoring in good risk surgical patients reveal that the administration of Norcuron® in doses up to three times that needed to produce clinical relaxation (0.15 mg/kg) did not produce clinically significant changes in systolic, diastolic or mean arterial pressure. The heart rate, under similar monitoring, remained unchanged. In some studies and was lowered by a mean of up to 8% in other studies. A large dose of 0.28 mg/kg administered during a period of no stimulation, while patients were being prepared for coronary artery bypass grafting, was not associated with alterations in rate-pressure-product or pulmonary capillary wedge pressure. Systemic vascular resistance was lowered slightly and cardiac output was increased insignificantly. (The drug has not been studied in patients with hemodynamic dysfunction secondary to cardiac valvular disease). Limited clinical experience (3 patients) with use of Norcuron® during surgery for pheochromocytoma has shown that administration of this drug is not associated with changes in blood pressure or heart rate.

Unlike other nondepolarizing skeletal muscle relaxants, Norcuron® has no clinically significant effects on hemodynamic parameters and will not counteract those hemodynamic changes or known side effects produced by or associated with anesthetic agents.

Preliminary data on histamine assay in 16 patients and available clinical experience in more than 600 patients indicate that hypersensitivity reactions such as bronchospasm, flushing, redness, hypotension, tachycardia, and other reactions commonly associated with histamine release are unlikely to occur.

INDICATIONS AND USAGE: Norcuron® is indicated as an adjunct to general anesthesia, to facilitate endotracheal intubation and to provide skeletal muscle relaxation during surgery or mechanical ventilation.

CONTRAINDICATIONS: None known.

WARNINGS: NORCURON® SHOULD BE ADMINISTERED IN CAREFULLY ADJUSTED DOSE BY OR UNDER THE SUPERVISION OF EXPERIENCED CLINICIANS WHO ARE FAMILIAR WITH ITS ACTIONS AND THE POSSIBLE COMPLICATIONS THAT MIGHT OCCUR FOLLOWING ITS USE. THE DRUG SHOULD NOT BE ADMINISTERED UNLESS FACILITIES FOR INTUBATION, ARTIFICIAL RESPIRATION, OXYGEN THERAPY, AND REVERSAL AGENTS ARE IMMEDIATELY AVAILABLE. THE CLINICIAN MUST BE PREPARED TO ASSIST OR CONTROL RESPIRATION. In patients who are known to have myasthenia gravis or the myasthenic (Eaton-Lambert) syndrome, small doses of Norcuron® may have profound effects. In such patients, a peripheral nerve stimulator and use of a small test dose may be of value in monitoring the response to administration of muscle relaxants.

PRECAUTIONS: **Renal Failure:** Norcuron® is well-tolerated without clinically significant prolongation of neuromuscular blocking effect in patients with renal failure who have been optimally prepared for surgery by dialysis. Under emergency conditions in anephric patients some prolongation of neuromuscular blockade may occur; therefore, if anephric patients cannot be prepared for non-elective surgery, a lower initial dose of Norcuron® should be considered. **Altered Circulation:** Time: Conditions associated with slower circulation time in cardiovascular disease, old age, edematous states resulting in increased volume of distribution may contribute to a delay in onset time; therefore dosage should not be increased.

Hepatic Disease: Limited experience in patients with cirrhosis or cholestasis has revealed prolonged recovery time in keeping with the role the liver plays in Norcuron® metabolism and excretion (see Pharmacokinetics). Data currently available do not permit dosage recommendations in patients with impaired liver function.

UNDER THE ABOVE CONDITIONS, USE OF A PERIPHERAL NERVE STIMULATOR FOR ADEQUATE MONITORING OF NEUROMUSCULAR BLOCKING EFFECT WILL PRECLUDE INADEQUATE EXCESS DOSING.

Severe Obesity or Neuromuscular Disease: Patients with severe obesity or neuromuscular disease may pose a unique and/or ventilatory problems requiring special care before, during and after the use of neuromuscular blocking agents such as Norcuron®.

Malfunction Hypertension: Many drugs used in anesthetic practice are suspected of being capable of triggering a potentially fatal hypertensive crisis in animals known as malignant hypertension. There are insufficient data derived from screening in susceptible animals (swine) to establish whether or not Norcuron® is capable of triggering malignant hypertension.

Norcuron® has no known effect on consciousness, the pain threshold or cerebation. Administration must be accompanied by adequate anesthesia.

Drug Interactions: Prior administration of succinylcholine may enhance the neuromuscular blocking effect of Norcuron® (vecuronium bromide) injection and its duration of action. If succinylcholine is used before Norcuron®, the administration of Norcuron® should be delayed until the succinylcholine effect shows signs of wearing off. With succinylcholine as the intubating agent, initial doses of 0.04-0.06 mg/kg of Norcuron® may be administered to produce complete neuromuscular block with clinical duration of action of 25-30 minutes (see CLINICAL PHARMACOLOGY). The use of Norcuron® before succinylcholine, in order to attenuate some of the side effects of succinylcholine, has not been sufficiently studied.

Other nondepolarizing neuromuscular blocking agents (pancuronium, d-tubocurarine, metocurine, and gallamine) act in the same fashion as does Norcuron®; therefore these drugs and Norcuron® may manifest an additive effect when used together. There are insufficient data to support concomitant use of Norcuron® and other competitive muscle relaxants in the same patient.

Inhalational Anesthetics: Use of volatile inhalational anesthetics such as enflurane, isoflurane, and halothane with Norcuron® will enhance neuromuscular blockade. Potentiation is most prominent with use of enflurane and isoflurane. With the above agents the initial dose of Norcuron® may be the same as with balanced anesthesia unless the inhalational anesthetic has been administered for a sufficient time at a sufficient dose to have reached clinical equilibrium (see CLINICAL PHARMACOLOGY).

Antibiotics: Parenteral/intraperitoneal administration of high doses of certain antibiotics may intensify or produce neuromuscular block on their own. The following antibiotics have been associated with various degrees of paralysis: aminoglycosides (such as neomycin, streptomycin, kanamycin, gentamicin, and dihydrostreptomycin); tetracyclines; bacitracin; polymyxin B; colistin; and sodium colistimethate. If these or other newly introduced antibiotics are used in conjunction with Norcuron® during surgery, unexpected prolongation of neuromuscular block should be considered a possibility. Other: Experience concerning injection of quinine during recovery from use of other muscle relaxants suggests that recurrent paralysis may occur. This possibility must also be considered for Norcuron®. Norcuron® induced neuromuscular blockade has been counteracted by alkalosis and enhanced by acidosis in experimental animals (cat). Electrolyte imbalance and diseases which lead to electrolyte imbalance, such as adrenal cortical insufficiency, have been shown to alter neuromuscular blockade. Depending on the nature of the imbalance, either enhancement or inhibition may be expected. Magnesium salts, administered for the management of toxemia of pregnancy, may enhance the neuromuscular blockade.

Drug/Laboratory Test Interactions: None known.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Long-term studies in animals have not been performed to evaluate carcinogenic or mutagenic potential or impairment of fertility.

Pregnancy: Pregnancy Category C: Animal reproduction studies have not been conducted with Norcuron®. It is also not known whether Norcuron® can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Norcuron® should be given to a pregnant woman only if clearly needed.

Pediatric Use: Infants under 1 year of age but older than 7 weeks, also tested under halothane anesthesia, are moderately more sensitive to Norcuron® on a mg/kg basis than adults and take about 1/2 times as long to recover. Information presently available does not permit recommendations for usage in neonates.

ADVERSE REACTIONS: Norcuron® was well-tolerated and produced no adverse reactions during extensive clinical trials. The most frequent adverse reaction to nondepolarizing blocking agents as a class consists of an extension of the drug's pharmacological action beyond the time period needed for surgery and anesthesia. This may vary from skeletal muscle weakness to profound and prolonged skeletal muscle paralysis resulting in respiratory insufficiency or apnea.

Inadequate reversal of the neuromuscular blockade, although not yet reported, is possible with Norcuron® as with all curariform drugs. These adverse reactions are managed by manual or mechanical ventilation until recovery is judged adequate. Little or no increase in intensity of blockade or duration of action of Norcuron® is noted from the use of theobromine, narcotic analgesics, nitrous oxide, or droperidol. See OVERDOSAGE for discussion of other drugs used in anesthetic practice which also cause respiratory depression.

OVERDOSAGE: There has been no experience with Norcuron® overdosage. The possibility of iatrogenic overdosage can be minimized by carefully monitoring muscle twitch response to peripheral nerve stimulation.

Excessive doses of Norcuron® can be expected to produce enhanced pharmacological effects. Residual neuromuscular blockade beyond the time period needed for surgery and anesthesia may occur with Norcuron® as with other neuromuscular blockers. This may be manifested by skeletal muscle weakness, decreased respiratory reserve, low tidal volume, or apnea. A peripheral nerve stimulator may be used to assess the degree of residual neuromuscular blockade and help to differentiate residual neuromuscular blockade from other causes of decreased respiratory reserve.

Respiratory depression may be due either wholly or in part to other drugs used during the conduct of general anesthesia such as narcotics, thiobarbiturates and other central nervous system depressants. Under such circumstances the primary treatment is maintenance of a patent airway and manual or mechanical ventilation until complete recovery of normal respiration is assured. Regonol® (pyridostigmine bromide injection), neostigmine, or edrophonium, in conjunction with atropine or glycopyrrolate will usually antagonize the skeletal muscle relaxant action of Norcuron®. Satisfactory reversal can be judged by adequacy of skeletal muscle tone and by adequacy of respiration. A peripheral nerve stimulator may also be used to monitor restoration of twitch height. Failure of prompt reversal (within 30 minutes) may occur in the presence of extreme debilitation, cachectic states, and with concomitant use of certain broad spectrum antibiotics, or anesthetic agents and other drugs which enhance neuromuscular blockade or cause respiratory depression of their own. Under such circumstances the management is the same as that of prolonged neuromuscular blockade. Ventilation must be supported by artificial means until the patient has resumed control of his respiration. Prior to the use of reversal agents, reference should be made to the specific package insert of the reversal agent.

DOSAGE AND ADMINISTRATION: Norcuron® (vecuronium bromide) injection is for intravenous use only. This drug should be administered by or under the supervision of experienced clinicians familiar with the use of neuromuscular blocking agents. Dosage must be individualized in each case. The dosage information which follows is derived from studies based upon units of drug per unit of body weight and is intended to serve as a guide only, especially regarding enhancement of neuromuscular blockade of Norcuron® by volatile anesthetics and by prior use of succinylcholine (see PRECAUTIONS/Drug Interactions). Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

To obtain maximum clinical benefits of Norcuron® and to minimize the possibility of overdosage, the monitoring of muscle twitch response to peripheral nerve stimulation is advised.

The recommended initial dose of Norcuron® is 0.08 to 0.10 mg/kg (1.4 to 1.75 times the ED₅₀) given as an intravenous bolus injection. This dose can be expected to produce good or excellent non-emergency intubation conditions in 2.5 to 3.0 minutes after injection. Under balanced anesthesia, clinically required neuromuscular blockade lasts approximately 25-30 minutes, with recovery to 25% of control achieved approximately 25 to 40 minutes after injection and recovery to 95% of control achieved approximately 45-65 minutes after injection. In the presence of potent inhalational anesthetics, the neuromuscular blocking effect of Norcuron® is enhanced. If Norcuron® is first administered more than 5 minutes after the start of inhalation agent or when steady state has been achieved, the initial Norcuron® dose may be reduced by approximately 15%, i.e., 0.060 to 0.085 mg/kg.

Prior administration of succinylcholine may enhance the neuromuscular blocking effect and duration of action of Norcuron®. If intubation is performed using succinylcholine, a reduction of initial dose of Norcuron® to 0.04-0.06 mg/kg with inhalation anesthesia and 0.05-0.06 mg/kg with balanced anesthesia may be required.

During prolonged surgical procedures, maintenance doses of 0.010 to 0.015 mg/kg of Norcuron® are recommended; after the initial Norcuron® injection, the first maintenance dose will generally be required within 25 to 40 minutes. However, clinical criteria should be used to determine the need for maintenance doses. Since Norcuron® lacks clinically important cumulative effects, subsequent maintenance doses, if required, may be administered at relatively regular intervals for each patient, ranging approximately from 12 to 15 minutes under balanced anesthesia, slightly longer under inhalation agents. (If less frequent administration is desired, higher maintenance doses may be administered.)

Should there be reason for the selection of larger doses in individual patients, initial doses ranging from 0.15 mg/kg up to 0.28 mg/kg have been administered during surgery under halothane anesthesia without ill effects to the cardiovascular system being noted as long as ventilation is properly maintained (see CLINICAL PHARMACOLOGY).

Dosage in Children: Older children (10 to 17 years of age) have approximately the same dosage requirements (mg/kg) as adults and may be managed the same way. Younger children (1 to 10 years of age) may require a slightly higher initial dose and may also require supplementation slightly more often than adults. Infants under one year of age but older than 7 weeks are moderately more sensitive to Norcuron® on a mg/kg basis than adults and take about 1/2 times as long to recover. See also subsection of PRECAUTIONS/Use Pediatric Use. Information presently available does not permit recommendation on usage in neonates (see PRECAUTIONS).

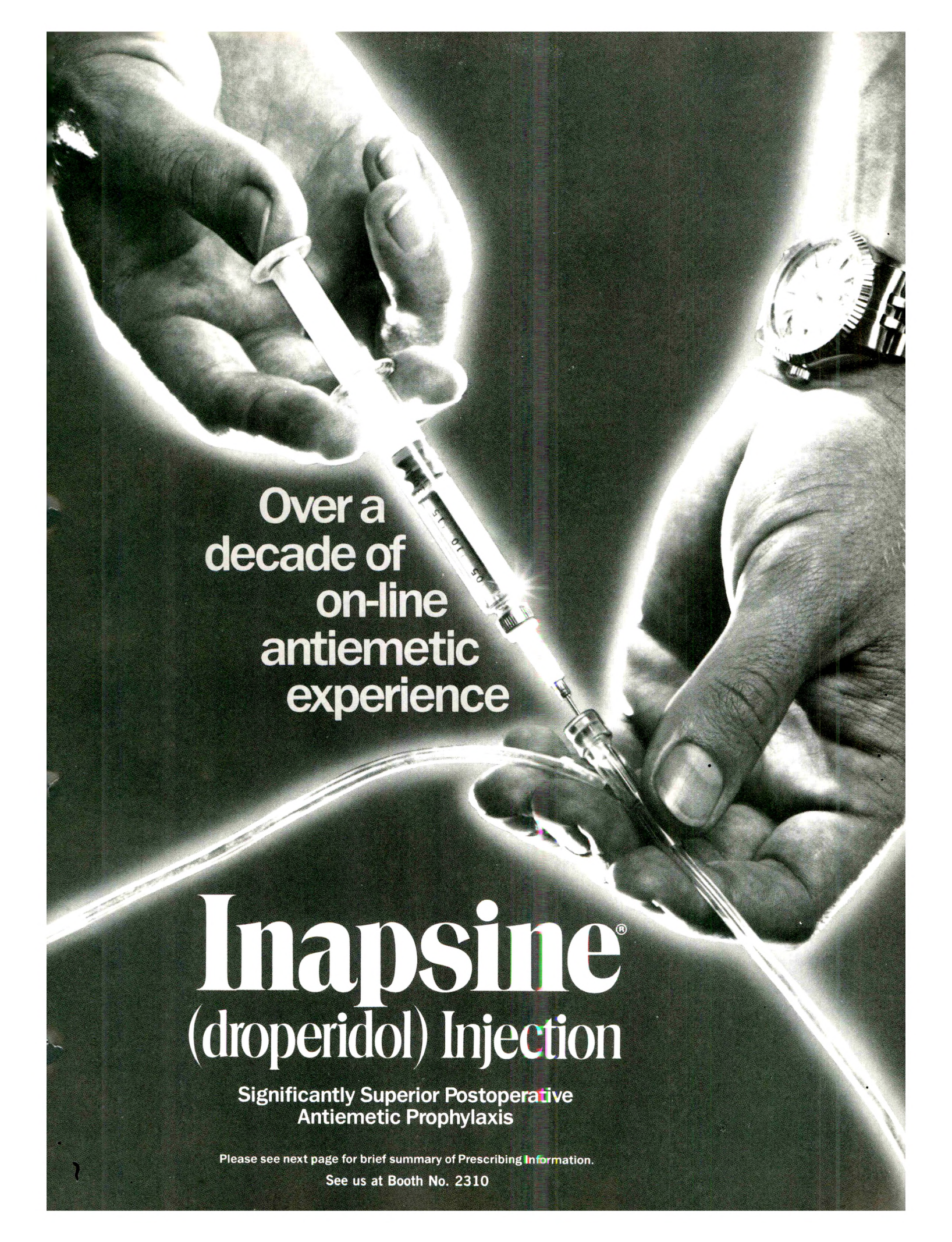
COMPATIBILITY: Norcuron® is compatible in solution with:

0.9% NaCl solution
5% glucose in saline
5% glucose in water
HOW SUPPLIED: 5 ml vials (contains 10 mg of active ingredient) and 5 ml ampul of preservative-free sterile water for injection as the diluent. Boxes of 10 (NDC#0052-0442-17).
5 ml vials (contains 10 mg of active ingredient) only. DILUENT (Sterile Water for Injection, USP) NOT SUPPLIED. Boxes of 10 (NDC#0052-0442-57).

STORAGE: PROTECT FROM LIGHT. Store at 15°-30°C (59°-86°F).
AFTER RECONSTITUTION: Solution may be stored in refrigerator or kept at room temperature not to exceed 30°C (86°F). DISCARD SOLUTION AFTER 24 HOURS. DISCARD UNUSED PORTION. SINGLE USE VIALS.
Manufactured for ORGANON INC. by BEN VENUE LABORATORIES, INC., Bedford, OH 44146 ISSUED 5/86



ORGANON INC.
WEST ORANGE, NEW JERSEY 07052



Over a
decade of
on-line
antiemetic
experience

Inapsine[®] (droperidol) Injection

Significantly Superior Postoperative
Antiemetic Prophylaxis

Please see next page for brief summary of Prescribing Information.

See us at Booth No. 2310

Over a decade of on-line antiemetic experience

Inapsine[®] (droperidol) Injection

Significantly Superior Postoperative Antiemetic Prophylaxis

- Proven in double-blind studies to provide postoperative antiemetic effect (when given perioperatively) that is significantly superior to placebo,^{1,2} diazepam² and hydroxyzine^{2,3}
- Potent antiemetic activity extends through discharge from recovery room
- May be administered intraoperatively in long procedures as well as preoperatively in both long and short procedures
- Helps protect against the pressor and arrhythmogenic effects of epinephrine
- Facilitates a comfortable, anxiety-free emergence, reducing the need for postoperative opioids

Before prescribing please consult complete prescribing information, of which the following is a brief summary.
Protect from light. Store at room temperature.
FOR INTRAVENOUS OR INTRAMUSCULAR USE ONLY.
Droperidol is a neuroleptic (tranquilizer) agent.

DESCRIPTION: 2 ml. and 5 ml. ampoules: Each ml. contains Droperidol 2.5 mg. and lactic acid for pH adjustment to 3.4 ± 0.4 . 10 ml. vials: Each ml. contains Droperidol 2.5 mg. with 1.8 mg. methylparaben and 0.2 mg. propylparaben, and lactic acid for pH adjustment to 3.4 ± 0.4 .

INDICATIONS: INAPSINE (droperidol) is indicated: • to produce tranquilization and to reduce the incidence of nausea and vomiting in surgical and diagnostic procedures; • for premedication, induction, and as an adjunct in the maintenance of general and regional anesthesia; • in neurolept analgesia in which INAPSINE (droperidol) is given concurrently with a narcotic analgesic, such as SUBLIMAZE* (fentanyl) injection, to aid in producing tranquility and decreasing anxiety and pain.

CONTRAINDICATIONS: INAPSINE (droperidol) is contraindicated in patients with known intolerance to the drug.

WARNINGS: FLUIDS AND OTHER COUNTERMEASURES TO MANAGE HYPOTENSION SHOULD BE READILY AVAILABLE. As with other CNS depressant drugs, patients who have received INAPSINE (droperidol) should have appropriate surveillance.

If INAPSINE (droperidol) is administered with a narcotic analgesic such as SUBLIMAZE (fentanyl), the user should familiarize himself with the special properties of each drug, particularly the widely differing durations of action. In addition, when such a combination is used, resuscitative equipment and a narcotic antagonist should be readily available to manage apnea. See package insert for fentanyl before using. Narcotic analgesics such as SUBLIMAZE (fentanyl) may cause muscle rigidity, particularly involving the muscles of respiration. This effect is related to the speed of injection. Its incidence can be reduced by the use of slow intravenous injection. Once this effect occurs, it is managed by the use of assisted or controlled respiration and, if necessary, by a neuromuscular blocking agent compatible with the patient's condition.

The respiratory depressant effect of narcotics persists longer than their measured analgesic effect. When used with INAPSINE (droperidol), the total dose of all narcotic analgesics administered should be considered by the practitioner before ordering narcotic analgesics during recovery from anesthesia. It is recommended that narcotics, when required, be used initially in reduced doses as low as $\frac{1}{4}$ to $\frac{1}{2}$ those usually recommended.

PRECAUTIONS: The initial dose of INAPSINE (droperidol) should be appropriately reduced in elderly, debilitated and other poor-risk patients. The effect of the initial dose should be considered in determining incremental doses. Certain forms of conduction anesthesia, such as spinal anesthesia and some peridural anesthetics, can cause peripheral vasodilatation and hypotension because of sympathetic blockade. Through other mechanisms, INAPSINE (droperidol) can also alter circulation. Therefore, when INAPSINE (droperidol) is used to supplement these forms of anesthesia, the anesthetist should be familiar with the physiological alterations involved, and be prepared to manage them in the patients selected for this form of anesthesia.

If hypotension occurs, the possibility of hypovolemia should be considered and managed with appropriate parenteral fluid therapy. Repositioning the patient to improve venous return to the heart should also be considered when operative conditions permit. It should be noted that in spinal and peridural anesthesia, tilting the

patient into a head down position may result in a higher level of anesthesia than is desirable, as well as impair venous return to the heart. Care should be exercised in moving and positioning of patients because of the possibility of orthostatic hypotension. If volume expansion with fluids plus other countermeasures do not correct the hypotension, then the administration of pressor agents other than epinephrine should be considered. Epinephrine may paradoxically decrease the blood pressure in patients treated with INAPSINE (droperidol) due to the alpha-adrenergic blocking action of droperidol.

Since INAPSINE (droperidol) may decrease pulmonary arterial pressure, this fact should be considered by those who conduct diagnostic or surgical procedures where interpretation of pulmonary arterial pressure measurements might determine final management of the patient. Vital signs should be monitored routinely.

Other CNS depressant drugs (e.g. barbiturates, tranquilizers, narcotics, and general anesthetics) have additive or potentiating effect with INAPSINE (droperidol). When patients have received such drugs, the dose of INAPSINE (droperidol) required will be less than usual. Likewise, following the administration of INAPSINE (droperidol), the dose of other CNS depressant drugs should be reduced.

INAPSINE (droperidol) should be administered with caution to patients with liver and kidney dysfunction because of the importance of these organs in the metabolism and excretion of drugs.

When the EEG is used for postoperative monitoring, it may be found that the EEG pattern returns to normal slowly.

Since INAPSINE (droperidol) is frequently used with the narcotic analgesic SUBLIMAZE (fentanyl), it should be noted that fentanyl may produce bradycardia, which may be treated with atropine; however, fentanyl should be used with caution in patients with cardiac bradyarrhythmias. (See full prescribing information for complete description.)

ADVERSE REACTIONS: The most common adverse reactions reported to occur with INAPSINE (droperidol) are mild to moderate hypotension and occasionally tachycardia, but these effects usually subside without treatment. If hypotension occurs and is severe or persists, the possibility of hypovolemia should be considered and managed with appropriate parenteral fluid therapy. Postoperative drowsiness is also frequently reported.

Extrapyramidal symptoms (dystonia, akathisia, and oculogyric crisis) have been observed following administration of INAPSINE (droperidol). Restlessness, hyperactivity, and anxiety which can be either the result of inadequate dosage of INAPSINE (droperidol) or a part of the symptom complex of akathisia may occur. When extrapyramidal symptoms occur, they can usually be controlled with anti-parkinson agents.

Other adverse reactions that have been reported are dizziness, chills and/or shivering, laryngospasm, bronchospasm and post-operative hallucinatory episodes (sometimes associated with transient periods of mental depression).

When INAPSINE (droperidol) is used with a narcotic analgesic such as SUBLIMAZE (fentanyl), respiratory depression, apnea, and muscular rigidity can occur if these remain untreated, respiratory arrest could occur.

Elevated blood pressure, with or without pre-existing hypertension, has been reported following administration of INAPSINE (droperidol) combined with SUBLIMAZE (fentanyl) or other parenteral analgesics. This might be due to unexplained alterations in sympathetic activity following large doses; however, it is also frequently attributed to anesthetic or surgical stimulation during light anesthesia.

DOSAGE AND ADMINISTRATION: Dosage should be individualized. Some of the factors to be considered in determining the dose are age, body weight, physical status, underlying pathological condition, use of other drugs, type of anesthesia to be used, and the surgical procedure involved.

Vital signs should be monitored routinely.

Usual Adult Dosage

- Premedication—(to be appropriately modified in the elderly, debilitated, and those who have received other depressant drugs) 2.5 to 10 mg. (1 to 4 ml.) may be administered intramuscularly 30 to 60 minutes preoperatively.
- Adjunct to General Anesthesia
Induction—2.5 mg. (1 ml.) per 20 to 25 pounds may be administered (usually intravenously) along with an analgesic and/or general anesthetic. Smaller doses may be adequate. The total amount of INAPSINE (droperidol) administered should be titrated to obtain the desired effect based on the individual patient's response.
Maintenance—1.25 to 2.5 mg. (0.5 to 1 ml.) usually intravenously (see warning regarding use with concomitant narcotic analgesic medication and the possibility of widely differing durations of action).

If INNOVAR* injection is administered in addition to INAPSINE (droperidol), the calculation of the recommended dose of INAPSINE (droperidol) should include the droperidol contained in the INNOVAR injection. See INNOVAR injection Package Insert for full prescribing information.

- Use Without A General Anesthetic In Diagnostic Procedures—Administer the usual I.M. premedication 2.5 to 10 mg. (1 to 4 ml.) 30 to 60 minutes before the procedure. Additional 1.25 to 2.5 mg. (0.5 to 1 ml.) amounts of INAPSINE (droperidol) may be administered, usually intravenously (see warning regarding use with concomitant narcotic analgesic medication and the possibility of widely differing durations of action).

Note: When INAPSINE (droperidol) is used in certain procedures, such as bronchoscopy, appropriate topical anesthesia is still necessary.

- Adjunct to Regional Anesthesia—2.5 to 5 mg. (1 to 2 ml.) may be administered intramuscularly or slowly intravenously when additional sedation is required.

How Supplied: 2 ml. and 5 ml. ampoules—packages of 10; 10 ml. multiple-dose vials—packages of 10.

U.S. Patent No. 3,161,645

NDC 50458-010-02; NDC 50458-010-05; NDC 50458-010-10

March 1980, Revised June 1980 IP41C98-M

Manufactured by TAYLOR PHARMACEUTICAL CO. for



JANSSEN
PHARMACEUTICA

Janssen Pharmaceutica Inc., Piscataway New Jersey 08854

REFERENCES: 1. Patton CM Jr, Moon MR, Dannemiller FJ. The prophylactic antiemetic effect of droperidol. *Anesth Analg* 1974;53:361-364.
2. Torretta FJ. A comparison of droperidol, diazepam, and hydroxyzine hydrochloride as premedication. *Anesth Analg* 1977;56:496-500.
3. Mehta P, Thonet E, Mehrotra D, et al. Comparative evaluation of preanesthetic medications. *Curr Ther Res* 1984;35:715-720.

© Janssen Pharmaceutica Inc. 1986 JPI-627R

Classified Advertising

PERMANENT POSITION WANTED

CRNA—experienced, wishes busy situation, solo or group, best of remuneration. 1-800-521-6750.

MDAS OR CRNAS: TRANS-AMERICAN ANESTHETISTS, WEST

Temporary or Permanent MDAs, CRNAs, ready to serve you, up-to-date skills, cooperative, licensed, insured professionals caring about you. Call 1-800-762-1258, Box 24432, Colorado Springs, CO 80918, or 303-598-2788 (CO).

ANESTHESIOLOGISTS

Excellent, prequalified individuals available to join your group on a career or temporary basis. For more information please contact: Southwest Anesthesia Services, PO Box 5719, Santa Fe, New Mexico 87502, (505) 983-7371.

ROCKY MTS./SOUTHWEST

We have career and temporary positions available from solo to large group practice in the Rocky Mts. and Southwest. Expenses paid; partnerships usually available. Please contact Southwest Anesthesia Services, PO Box 5719, Santa Fe, NM 87501. (505) 983-7371.

800-FAST GAS: WORLDWIDE ANESTHESIA

Have you got knocks and pings in your Anesthesia Department? Whether it's a short or long-term staff shortage . . . we've got quality MDs and CRNAs to get your program running smoothly! 1-800-327-8427 Worldwide Anesthesia, John Paju, President.

TUTORING FOR WRITTEN AND ORAL BOARD EXAMS:

Individual or small group sessions given in New York City, San Francisco, and Palm Springs. Unique approach to development of test-taking skills, including mock orals. Basic science emphasis. Call 415-321-1117 or reply to Box K23, % *Anesthesia and Analgesia*, Desk Editorial, 52 Vanderbilt Avenue, New York, NY 10017. Include phone number in response.

VERMONT

BC/BE anesthesiologist to join 2 MD, 2 CRNA group in central Vermont at 180-bed hospital. No open heart or neurosurgery. Prefer experience with regional techniques. Excellent recreational facilities. Please send CV to Chairman, Department of Anesthesia, Central Vermont Hospital, PO Box 547, Barre, VT 05641.

LOUISIANA: FACULTY ANESTHESIOLOGISTS

Louisiana State University School of Medicine in Shreveport has immediate openings for faculty personnel (BC/BE) of all levels in the Department of Anesthesiology. Academic rank commensurate with education and experience. Excellent financial and fringe benefits offered at all ranks. Shreveport, with a metropolitan area population of 350,000, has a progressive, growing and expanding medical school with an extremely challenging high risk patient population. An active transplant service is in operation. Please send current CV along with your inquiry to Norman H. Blass, MD, Professor and Chairman, Department of Anesthesiology, Louisiana State University School of Medicine, 1501 Kings Highway, Shreveport, LA 71130-3932. Affirmation Action/Equal Opportunity Employer.

PRIVATE TUTORING AVAILABLE FOR WRITTEN AND ORAL BOARD EXAMS

Send name, address, and phone to Box ANA 5-84-E, % *Anesthesia and Analgesia*, Desk Editorial, Elsevier Science Publishing Co., Inc., 52 Vanderbilt Avenue, New York, NY 10017.

ANESTHESIOLOGIST SEEKING CHAIRMAN

for established anesthesia department in 400-bed suburban Chicago, Illinois hospital. All surgical specialties represented, including open heart. Must be board certified with 7 yr minimum in academic environment. Excellent financial arrangements. Send CV to CSS Associates, 6819 Winston Drive, Tinley Park, Illinois 60477.

NEW HAMPSHIRE

Group of anesthesiologists seek CRNA or PA anesthetist. Must be qualified in all modes of anesthesia, including regional. Lovely Southern NH community. Convenient to recreational and cultural centers. Reply to Box W53, % *Anesthesia and Analgesia*, Desk Editorial, Elsevier Science Publishing Company, 52 Vanderbilt Avenue, New York, NY 10017.

ALABAMA

Several immediate openings. We are consultants for anesthesiologists and charge no placement fees. Send reply in confidence to Medical Management, Inc., PO Drawer 7308, Montgomery, AL 36107.

ARIZONA

Well-established dynamic group of anesthesiologists is expanding. We need anesthesiologists well-trained in all areas. We

are an aggressive group covering several hospitals. We need anesthesiologists immediately. Send CV to Anesthesia Center Associates, 3625 N. 16th Street #119, Phoenix Arizona 85016. (602)264-7410.

NEW ENGLAND

Immediate openings for BC/BE MDA in coastal New England town. No neuro or open heart. Income guarantee. NAMA, P.O. Box 24; Carlisle, MA 01741. (617) 369-5980.

TEXAS

Pediatric Anesthesiologist. Excellent opportunity available for BC/BE pediatric anesthesiologist with minimum 1 yr pediatric fellowship. Be second person in exciting practice serving two children's hospitals. Experience in pediatric cardiology, PICU, NICU, or pulmonary helpful. Hospitals offer all subspecialties. Must be eligible for Texas license (FLEX required). Benefits include competitive salary, malpractice, profit sharing leading to partnership. If living in a city filled with cultural, recreational, and academic facilities while practicing in two of the SW's finest hospitals appeals to you, submit a CV with three references to: Search Director, PO Box 2138, Fort Worth, TX 76113.

COOK COUNTY HOSPITAL DEPARTMENT OF ANESTHESIOLOGY

An opening for a Division Chairman of Pediatric Anesthesiology. Must be board certified in anesthesiology and have at least two yr experience in pediatric anesthesiology. Excellent administrative and teaching

CLASSIFIED ADS

Anesthesia and Analgesia makes available classified advertising space for those interested in obtaining positions, or wishing to announce meetings, postgraduate courses, or other events. Display space (minimum 1/4 page) is also available through Pharmaceutical Media, Inc. Rates for classified advertising: **\$1.00 per word, minimum twenty words. Additional fee of \$12.00 for box number ads.** Copy deadline 7 weeks prior to publication, e.g., for the March issue, copy should be received by the 1st of January. Full payment or institutional purchase order must accompany the copy for each ad. Ads received without a check or purchase order will be returned. Ad copy, subject to acceptance by publisher, should be typed double-spaced and mailed in duplicate to:
Anesthesia and Analgesia
Desk Editorial
Classified Ads
Elsevier Science Publishing Co, Inc,
52 Vanderbilt Avenue, New York, NY 10017.
Make checks payable to Elsevier Science Publishing Co, Inc.

abilities. Competitive salary and excellent fringe benefits. Send CV to or call Dr. Radha Kartha, Acting Chairperson, Department of Anesthesiology, Cook County Hospital, 1925 West Harrison Street, Chicago, IL 60612. (312) 633-6176.

ANESTHESIOLOGIST

35 yr old. Board eligible. Available immediately. Proficient in all types of anesthesia. 3 yr experience after 4 yr of residency training. Respond to Box Y1, % *Anesthesia and Analgesia*, Desk Editorial, Elsevier Science Publishing Company, 52 Vanderbilt Avenue, New York, NY 10017.

SOUTHWESTERN PA ANESTHESIOLOGIST

BE/BC to join group. All except open heart. Opening immediately. Excellent compensation and future for right person. Response confidential. Pittsburgh area. Submit CV to Box L26, % *Anesthesia and Analgesia*, Desk Editorial, Elsevier Science Publishing Company, 52 Vanderbilt Avenue, New York, NY 10017.

NORTH CAROLINA

Anesthesiologist (BE/BC) wanted for thriving anesthesia practice in eastern North Carolina coastal plains city of 25,000 to join group of one MDA and three CRNAs in 200-bed hospital. All surgical subspecialties except Neuro and OH. Send CV to Box X60, % *Anesthesia and Analgesia*, Elsevier Science Publishing Company, Desk Editorial, 52 Vanderbilt Avenue, New York, NY 10017.

ANESTHESIOLOGIST

BE or BC to join growing central Alabama practice. All procedures except open heart. Two hospitals, 400+ bed and 75+ bed. Immediate opening. Excellent salary and benefits. All replies confidential. Send CV to Administrator, PO Box 6173, Montgomery, AL 36106.

NEW YORK: PEDIATRIC ANESTHESIOLOGIST
Expanding division of pediatric anesthesia, Department of Anesthesiology, Columbia

University College of Physicians and Surgeons, is seeking individuals at the Assistant Professor/Associate Professor level with training in anesthesia and pediatrics. Division responsibilities are in the operating room and intensive care unit. Applicants should possess board certification or eligibility, excellent clinical and teaching skills as well as research interests. Interested individuals should reply to: Peter Rothstein, MD, Director, Division of Pediatric Anesthesia, Box 62, Babies Hospital, 622 West 168th Street, New York, NY 10032. Columbia University takes affirmative action to ensure equal opportunity.

INDIANA

A position is available for a pediatric anesthesiologist at the assistant or associate professor level in the Department of Anesthesia, Indiana University School of Medicine. Candidates must have completed a specialized year in pediatric anesthesia and be in the examination system or board certified. Please send a curriculum vitae to Robert K. Stoelting, MD, Professor and Chairman, Department of Anesthesia, Fesler Hall Room 204, Indiana University School of Medicine, 1120 South Drive, Indianapolis, IN 46223. Indiana University is an Equal Opportunity Employer

INDIANA

Faculty positions are available at the Assistant and Associate Professor levels. All candidates for these positions must be in the examination system or board certified. Please send a curriculum vitae to Robert K. Stoelting, MD, Professor and Chairman, Department of Anesthesia, Fesler Hall, Room 204, Indiana University School of Medicine, 1120 South Drive, Indianapolis IN 46223. Indiana University is an Equal Opportunity employer

CHIEF OF ANESTHESIA

to head department serving 280-bed community hospital in Baltimore. Board certification required with administrative experience preferred. Position includes active

practice of anesthesiology and responsibility for quality assurance standards and smooth operation of anesthesia services in a busy OR. Reply to Box X59, % *Anesthesia and Analgesia*, Desk Editorial, Elsevier Science Publishing Company, 52 Vanderbilt Avenue, New York, NY 10017.

CALIFORNIA: ANESTHESIOLOGIST

Full-time faculty position at the Associate/Full Professor level in expanding, young department with emphasis on teaching and research. Complete clinical services in one hospital. Prerequisites include board certified; meet California license requirements; clinical expertise in neuro, pain and/or pediatrics; demonstrated ability as a research scientist and ability to write scholarly articles. Send curriculum vitae, bibliography and names of five references to John H. Eisele, JR., MD, Anesthesiology Department, University of California, Davis, Medical Center, 2315 Stockton Blvd., Sacramento, CA 95817. Position open until filled but not later than January 31, 1987. We are an Equal Opportunity/Affirmative Action Employer.

OB ANESTHESIOLOGISTS

Fellowship trained to work for PC at busy university-affiliated hospital. Stimulating practice. Home of regional perinatal center. 4,000+ deliveries/year. Excellent cultural, educational and recreational resources. Liberal salary and fringe benefits. Send CV with application to CNY Anesthesia Group, PC, 736 Irving Avenue, Syracuse, New York 13210.

NEW YORK

PG-4, CA-3 Fellowship Positions at Memorial Sloan-Kettering Cancer Center Beginning July 1987. Straight clinical and clinician-investigator opportunities available in: Critical Care Medicine, Pain Management and Anesthesia for Thoracic, Neuro and Head and Neck surgery. Send CV and summary of career goals to Robert F. Bedford, MD, Chairman, Department of Anesthesiology and Critical Care Medicine, Memorial Sloan-Kettering Cancer Center, 1275 York Avenue, New York, N.Y. 10021.

The Department of Anesthesiology and the
Page and William Black
Post Graduate School of Medicine of
The Mount Sinai Medical Center
announce a symposium:

ADVANCES IN ANESTHESIOLOGY
Clinical and Economic

January 17-24, 1987
Martinique, French West Indies

This course meets the criteria for 18 hours in
Category 1 of the Physicians Recognition Award
of the American Medical Association.

Program Directors: Joel A. Kaplan, M.D. and
George Silvey, M.D., Ph.D.

Faculty: Dawn Desiderio, M.D., Paul L. Goldiner,
M.D., Anthony D. Ivankovich, M.D., Olga Ivanko-
vich, M.D., Norman Sonnenklar, M.D., Allen
Unger, M.D., Barry L. Cliff, C.F.P., Scott Spell-
man.

For information, Please contact:

George Silvey, M.D., Ph.D. or	Allied Tours
Department of Anesthesiology	Mt. Sinai Seminar
Mount Sinai Medical Center	165 West 46th Street
One Gustave L. Levy Place	New York, NY 10036
New York, New York 10029	(212) 869-5100
(212) 650-5954	L. Gerber

AMBULATORY HEALTH CARE PHYSICIAN SURVEYORS

The Joint Commission on Accreditation of Hospi-
tals is seeking Anesthesiologists who are inter-
ested in working as Consultant Surveyors with
the accreditation program for ambulatory health
care.

Interested individuals must have a minimum of
five years clinical and administrative experience
in a freestanding ambulatory surgical center.

Consultant Surveyors must be available 20 to 25
days per year. Each survey lasts for approximately
one & one-half to two business days. Successful
applicants will be required to attend a three day
training program in early Spring 1987. Consul-
tants are reimbursed for full travel expenses and
receive a per diem or actual reimbursement for
hotel and meals, plus a Consultant fee for each
day spent on-site for the survey. Travel is on a
nationwide basis.

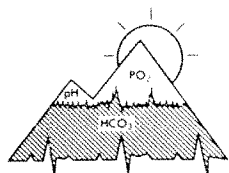
Interested candidates should send a current
resume to:

Peggy A. White
Associate Director Personnel
Surveyor Employment

Joint Commission
on Accreditation of Hospitals

875 N. Michigan Avenue
Chicago, IL 60611

Equal Opportunity Employer M/F



SIXTH ANNUAL CANADIAN WINTER ANAESTHESIA MEETING

Quebec City, Que
February 22-27, 1987

The Scientific Program includes a wide range of sub-
jects: O.B. Anesthesia, I.C.U., Pediatric Anesthesia,
Intraoperative Problems, and Trauma from the E.R. to
the O.R.

This Program is approved for A.M.A. Category 1
C.M.E. Credits.

The Scientific Program has been arranged to provide
ample time to explore this charming winter setting.

For further information, please write to:

Programme Chairman
Canadian Winter Anaesthesia Meeting
Department of Anaesthesia, Room 2303
The Hospital for Sick Children,
555 University Avenue,
Toronto, Ont. Canada M5G 1X8
or call: (416) 598-7445



CBE STYLE MANUAL

Fifth Edition

A guide for Authors, Editors, and Publishers in
the Biological Sciences

Widely accepted and recommended as the
standard reference for journals and books in the
biological sciences

- Special features of this newly updated and greatly expanded edition include:
- four new chapters;
 - reorganization of the "Manuscript Preparation" section for easier reference;
 - new conventions in the chapter on "Style in Special Fields";
 - complete revision of the section on "Plant Sciences";
 - cross-listing of "Abbreviations and Symbols";
 - and much more . . .

CONTENTS: Ethical conduct in authorship and publication • Planning the communication • Writing the article • Prose style for scientific writing • References • Illustrative materials • Editorial review of manuscripts • Application of copyright law • Manuscript into print • Proof correction • Indexing • General style conventions • Style in special fields • Abbreviations and symbols • Word usage • Secondary services for literature searching • Useful references with annotations • Subject index

ISBN: 0-914340-04-2; clothbound; publication date: September 1983; trim size 6 x 9 inches; 324 pages

Regular Price: \$24.00 (10% discount on 10 or more copies delivered to one address)

CBE Member Price: \$21.50 (single copy paid by personal check)

Terms of Sale: All sales final; no returns.

Prepayment required; U.S. currency drawn on a U.S. bank.

Price includes BOOK RATE postage.

For faster delivery--first class, air mail, or UPS available at additional charge (book weight 1 lb 9 oz).

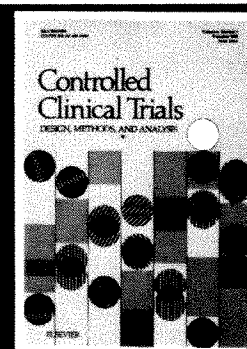
Maryland residents, please add 5% sales tax.

Mail your order with payment to:
COUNCIL OF BIOLOGY EDITORS, INC.
9650 Rockville Pike, Bethesda, MD 20814

*The recognized authority on mounting
and evaluating clinical trials*

Controlled Clinical Trials

Design, Methods, and Analysis
Official Journal of the Society for Clinical Trials



Editor-in-Chief

Curtis L. Meinert

Department of Epidemiology
Johns Hopkins School of Hygiene and Public Health
Baltimore, Maryland

Associate Editors

Niels Tygstrup

Rigshospitalet
Copenhagen, Denmark

O. Dale Williams

University of North Carolina
Chapel Hill, North Carolina

Controlled Clinical Trials is a respected and valuable source of information for clinicians and statisticians involved in mounting and monitoring clinical trials and long-term follow-up studies. Its articles focus on design features or organizational structures that have contributed to the success of other studies — from short-term, small-scale trials to long-term multicenter investigations — and can be beneficially applied to similar projects.

Controlled Clinical Trials offers proven methods for:

- calculating sample size for long-term trials
- determining patient compliance in ongoing trials

- monitoring clinical trials for adverse or beneficial effects
- assessing costs

Recognizing the importance of effective data management, **Controlled Clinical Trials** features articles on the critical design and operating components of data processing systems that are used for maintaining a long-term data base, and quality assurance methods for error detection in data generation and processing procedures.

1986 Subscription Information

Volume 7 (4 issues)

Institutional Rate: \$112.00

Personal Rate: \$56.00

For air delivery in the U.S., Canada, or Mexico, add \$17.00. Subscribers outside the U.S. should add \$12.00 for surface delivery (not available to Europe); \$11.00 for surface air lift delivery to Europe; \$16.00 for surface air-lift delivery to Japan; or \$38.00 for air delivery to the rest of the world.

Sample copies are available upon request.
ISSN 0197-2456

Controlled Clinical Trials is abstracted/indexed in:
Biological Abstracts, Current Contents/Life Sciences,
Excerpta Medica, and Index Medicus.

For sample copies, send to

In North and South America:

Elsevier Science Publishing Co., Inc.
P.O. Box 1663
Grand Central Station
New York, NY 10163-1663

in the rest of the world:

Elsevier Science Publishers
Direct Mail Department
P.O. Box 211
1000 AE Amsterdam
The Netherlands

Note: Send subscription orders to either your usual supplier or the New York address. All subscriptions begin with the first issue of the calendar year and are entered upon receipt of payment. Subscription rates valid until December 31, 1986.

EB 365

Elsevier

INDEX TO ADVERTISERS

American Critical Care	
<i>Hespan</i>	A8, A9, A10
Anaquest	
<i>Enlon</i>	A22, A23, A24
Bristol Laboratories	
<i>Stadol</i>	Cover 4
Classified Advertising.....	A33, A34
Cormed	
<i>Cormed II</i>	A2
Halocarbon Laboratories	
<i>Halothane</i>	A25
The Hospital for Sick Children	
<i>Continuing Education</i>	A35
Janssen Pharmaceutica	
<i>Inapsine</i>	A31, A32
<i>Sufenta</i>	A6, A7
Joint Commission on Accreditation of Hospitals	
<i>Employment Opportunities</i>	A35
Kettering Software Systems, Inc.	
<i>Software</i>	A11
Lawrence Medical	
<i>Continuous Cardiac Output Monitor</i>	A20, A21
Mount Sinai Medical Center	
<i>Continuing Education</i>	A35
North American Drager	
<i>Narkomed 3</i>	A38, Cover 3
Olympus Corporation	
<i>LF-1 Intubation Scope</i>	A17, A18
Organon Pharmaceuticals	
<i>Norcuron</i>	A27-A30
<i>Pavulon</i>	Cover 2
Physio-Control Corporation	
<i>Lifestat 1600</i>	A14, A15
Puritan-Bennett Corporation	
<i>PB245 Monitor</i>	A13
Sheridan Catheter Corporation	
<i>Tracheal Tubes</i>	A26

Advertising Office: Pharmaceutical Media, Inc., 130 Madison Avenue, 6th Floor, New York 10016. Telephone: (212) 685-5010

Narkomed *unparalleled power and performance*



Narkomed 3 is a new system combining the most reliable basic anesthesia delivery instrument with the most powerful and unique information and monitoring capability available anywhere. From the instant you energize the system... with a single switch... your control of Narkomed 3 can be classified as a breakthrough experience.

What's new about the patient-data displays?

Everything you see on this unique integrated and prioritized data-display screen is new. This is a sampling.

- Central Alarm Display, a tabulation in Warning, Caution, and Advisory format.
- Bargraph display of five important measurements for instant qualitative assessment.
- Central display for quantitative anesthesia documentation, with optional hardcopy presentation.
- Waveform display of respiratory measurements.
- Trending display of all anesthesia monitoring system measurements.

What is monitored by the Narkomed 3?

Six integrated monitors are available, from a total of eight, for display of patient-status data. Depending upon your choice, the information presented comprises...

- | | |
|--|--|
| <input type="checkbox"/> Oxygen Concentration | <input type="checkbox"/> Breathing Pressures |
| <input type="checkbox"/> Pulse Oximetry | <input type="checkbox"/> Carbon Dioxide |
| <input type="checkbox"/> Respiratory Volumes | <input type="checkbox"/> Blood Pressures |
| <input type="checkbox"/> Anesthesia Concentrations | <input type="checkbox"/> Temperatures |

The first two monitoring sources are standard. The other six monitors are optional. With an optional interface, certain other external monitors can be added.

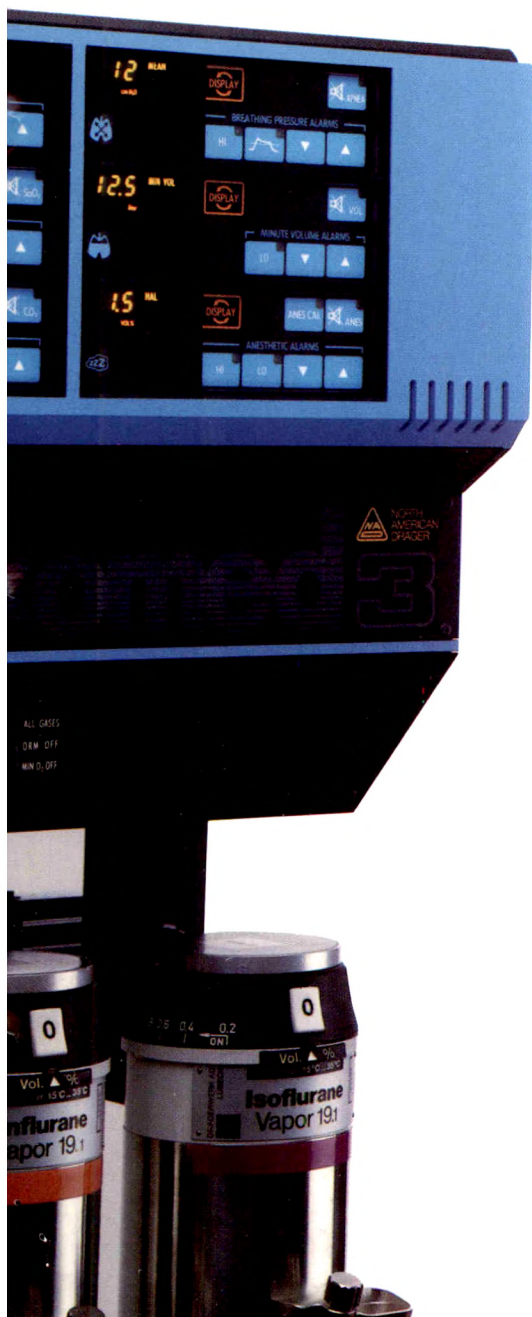
Why hasn't there been a system like this before?

Because the variety of monitors now available were introduced, by many different makers, over a period of more than ten years. Often, the information they provided was not used because it was not controlled, integrated, or prioritized. Now, the unique Narkomed 3 puts you in full control of the system, with less effort. Experience it now. Contact your NAD Dealer, or call us directly.



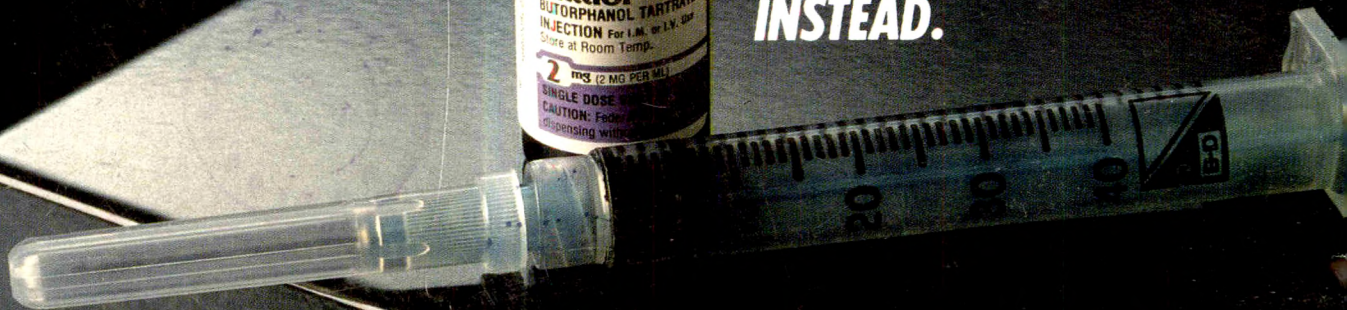
**NORTH
AMERICAN
DRÄGER**

148B Quarry Road
Telford, Pennsylvania 18969
(215) 723-9824
or 248-0834
TWX 510-661-6148
NOAMDRAGER TEL





INSTEAD.



BRISTOL®

© 1985 Bristol Laboratories
Division of Bristol-Myers Company
Syracuse, New York 13221-4755

Anesthesia and Analgesia

Acc.
16-12-87

Journal of the International Anesthesia Research Society
Oldest Publication in the Specialty—Established 1922



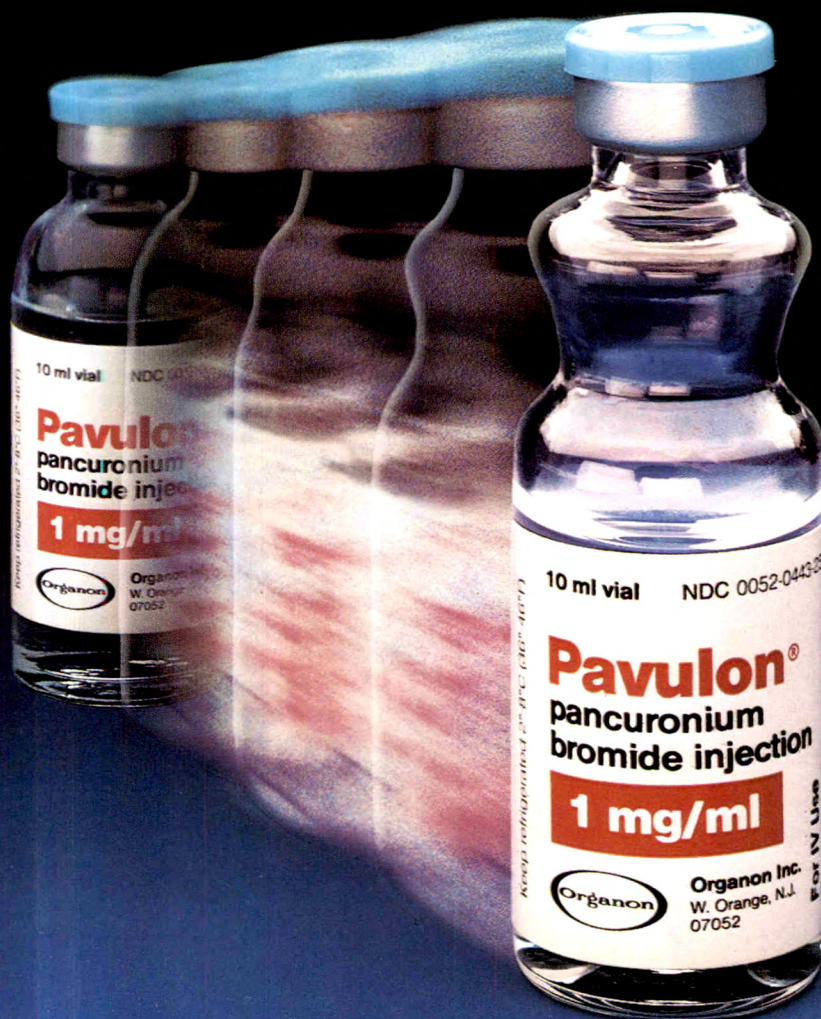
Organon presents:

The new, distinctive Pavulon[®] vial for positive identification and handling ease.

- New functionally contoured vial speeds selection and helps assure positive identification.
- Easy-grip, no-slip design for better handling.



- Now there is one more reason to choose PAVULON[®], with over 14 years of successful clinical experience.



Pavulon[®]
(pancuronium bromide
injection)

Now...tangibly different.





Anesthesia and Analgesia

Journal of the International Anesthesia Research Society

3645 Warrensville Center Road, Cleveland, Ohio 44122 Telephones: (216) 295-1124 or 295-1130

Editorial Board

Editor in Chief

Nicholas M. Greene, MD, New Haven, Connecticut

Editors

David R. Bevan, MA, MB, BChir,
Montreal, Quebec, Canada

D. Ryan Cook, MD, Pittsburgh, Pennsylvania

Benjamin G. Covino, PhD, MD, Boston, Massachusetts

Norig Ellison, MD, Philadelphia, Pennsylvania

Mieczyslaw Finster, MD, New York, New York

Alison B. Froese, MD, Kingston, Ontario, Canada

Edward D. Miller Jr, MD, New York, NY

Walter S. Nimmo, MD, BSc, FRCP, FFARCS,
Sheffield, United Kingdom

Daniel M. Philbin, MD, Boston, Massachusetts

J. Gerald Reves, MD, Durham, North Carolina

Petter A. Steen, MD, Oslo, Norway

John H. Tinker, MD, Iowa City, Iowa

K.C. Wong, MD, PhD, Salt Lake City, Utah

Book Review Editor

Norig Ellison, MD, Philadelphia, Pennsylvania

Editorial correspondence and manuscripts should be addressed to: NICHOLAS M. GREENE, MD, Editor in Chief, *Anesthesia and Analgesia*, Yale University School of Medicine, 333 Cedar Street, New Haven, Connecticut 06510 (Telephone: 203-785-4703). For information concerning preparation of manuscripts see "A Guide for Authors" published quarterly in the Journal. All articles published in this Journal become the property of the International Anesthesia Research Society. Reproduction in whole or part is not permitted except by written consent of the publisher and the author.

Books for review should be sent directly to the Book Review Editor, NORIG ELLISON, MD, Department of Anesthesia, University of Pennsylvania, Philadelphia, Pennsylvania 19104.

Reprints: For single copies, write directly to the senior author at the address listed on the title page. Quantity orders (minimum 100) processed through ELSEVIER SCIENCE PUBLISHING CO, INC, 52 Vanderbilt Avenue, New York, NY 10017, prices on request.

The International Anesthesia Research Society is a nonprofit, scientific, and educational corporation in the state of Ohio. Members of the Board of Trustees of the Society are: Douglas B. Craig, MD, Bruce F. Cullen, MD, E. Paul Didier, MD, Judith H. Donegan, MD, PhD, Noel W. Lawson, MD, John T. Martin, MD, Emerson A. Moffitt, MD, Dean H. Morrow, MD, Robert K. Stoeltz, MD, and John L. Waller, MD. Emeritus Trustees are: Paul R. Dumke, MD, Morris T. Nicholson, MD, B. B. Sankey, MD, and T. H. Seldon, MD.

Anesthesia and Analgesia (ISSN 0003-2999) is issued monthly for the IARS in one indexed volume per year by Elsevier Science Publishing Co, Inc, 52 Vanderbilt Avenue, New York, NY 10017. Printed in USA. © 1986 International Anesthesia Research Society. Second class postage paid at New York, NY and at additional offices.

Subscription information for 1986 applying to IARS members: USA and possessions, \$50.00 per year, in all other countries \$61.00. Membership is available to individuals with doctorate degrees in medicine, osteopathy, dentistry, veterinary medicine, or other disciplines who are engaged in active clinical practice of or research in anesthesiology. ASSOCIATE MEMBERSHIP is available to individuals certified, licensed, or accredited in anesthesia-related professions (CRNA, CRTT, RRT, Physician Assistant). EDUCATIONAL MEMBERSHIP (half the full member price) is available to interns, residents, students in nurse anesthesia and related training programs, for a 2- or 3-year period only upon completion of application including certification by applicant's program director.

All membership payments and correspondence regarding IARS member subscriptions should be sent to: Emerson A. Moffitt, MD, Executive Secretary, International Anesthesia Research Society, 3645 Warrensville Center Road, Cleveland, Ohio 44122.

Subscription information for 1986 applying to non-IARS members: Institutions, \$95.00; nonmember individuals, \$50.00. Outside of the USA and possessions, please add \$11.00 for surface postage and handling. For airmail, add \$40.00 in USA, Canada, and Mexico, \$23.00 for surface airmail to Europe, \$36.00 for surface airmail to Japan, and \$93.00 for airmail to the rest of the world. Postmaster: Send address changes to: *Anesthesia and Analgesia*, Elsevier Science Publishing Co, Inc, 52 Vanderbilt Avenue, New York, NY 10017.

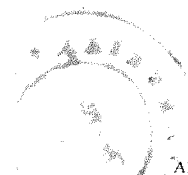
Orders and inquiries regarding institutional and nonmember individual subscriptions should be directed to: Journals Fulfillment, Elsevier Science Publishing Co, Inc, 52 Vanderbilt Avenue, New York, NY 10017. Subscriptions are entered for the calendar year, January-December.

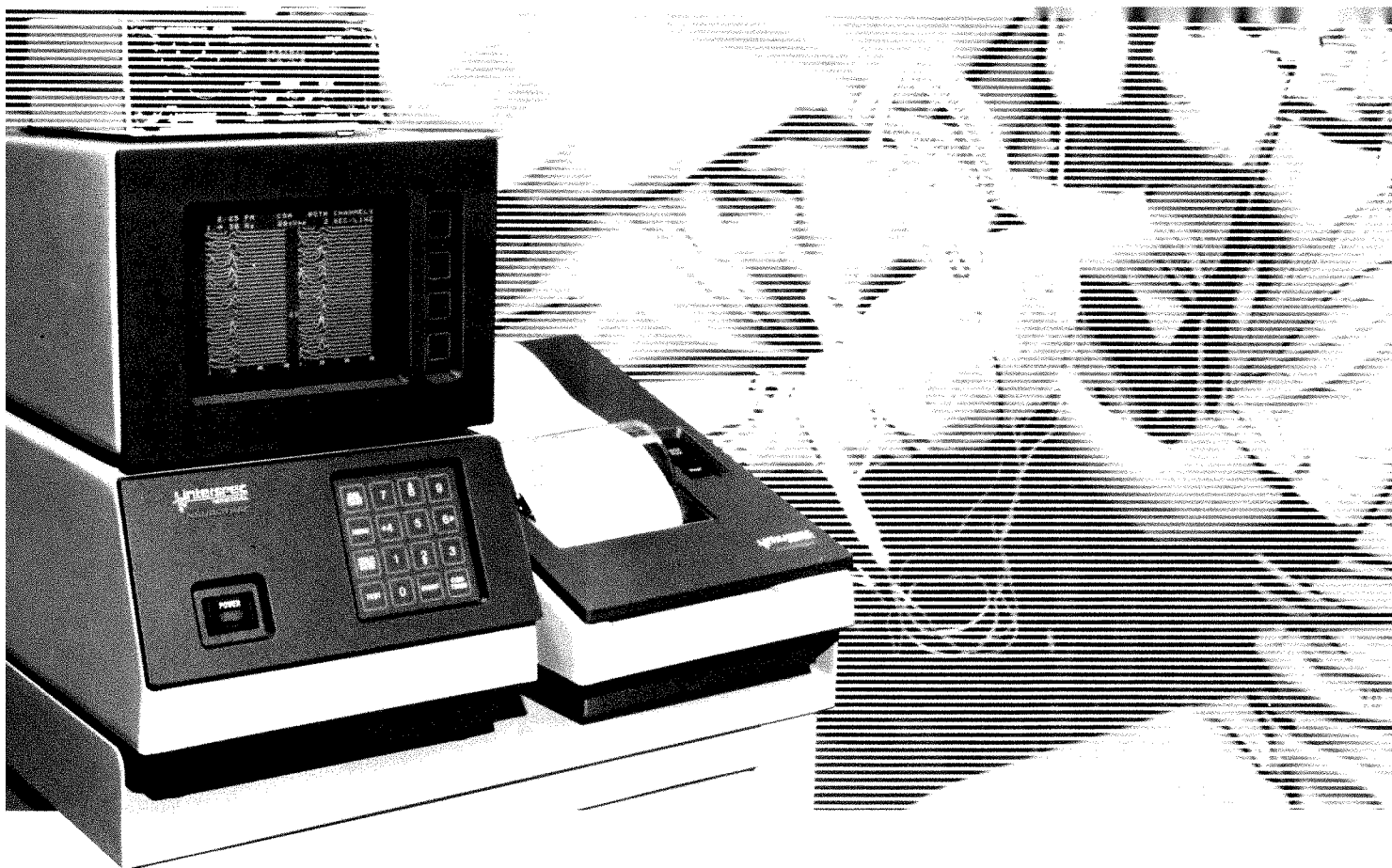
Correspondence inquiries regarding IARS member subscriptions should be sent to the IARS at the Cleveland, Ohio address above. Correspondence regarding all other subscriptions should be sent to Elsevier.

Advertising inquiries should be addressed to: Pharmaceutical Media, Inc, 130 Madison Avenue, New York, NY 10016. The appearance of advertising in publications of the International Anesthesia Research Society does not constitute a guarantee or endorsement of the quality or value of such product or of the claims made for it by its manufacturer. Discussions, views, and recommendations as to medical procedures, choice of drugs, and drug dosages are the responsibility of the authors. Every effort has been made to ensure the accuracy of the information. The editor, publisher, or the Society, however, must disclaim any responsibility or liability. Readers are advised to check package insert information for each drug before administration.

See classified ads section for submission of classified material.

Single issues: Single copy information available from Elsevier Science Publishing Co, Inc, upon request. Back volume (all issues prior to 1983) information available from IARS.





It Can Make The Critical Difference NEUROTRAC™

• For early detection of neurological change

A cerebral activity monitor should be in your operating room, recovery room, or any critical care area. Now it can be. NEUROTRAC is the most convenient device ever developed to accurately monitor cerebral activity. Using easily interpreted processed EEG, NEUROTRAC allows you to detect changes in EEG which can be caused by ischemia or other factors, thereby providing added protection. NEUROTRAC is in routine use on a worldwide basis during:

- ☐ carotid endarterectomy
- ☐ cardiopulmonary bypass
- ☐ induced hypotension
- ☐ barbiturate coma
- ☐ other conditions which could result in cerebral hypoxia

NEUROTRAC is the system that FITS:

Your Needs. NEUROTRAC'S automatic printout and multiple display formats supply the right information in the right form for you.

Neurotrac's somatosensory evoked potential option allows assessment of the functional integrity of neural pathways in orthopedic and neurosurgical procedures.

Your space. NEUROTRAC'S compact size fits easily into the OR or ICU.

Your budget. NEUROTRAC provides critical information at substantially less cost than conventional EEG.

**For more information
call TOLL FREE 1-800-356-0007**

Nicolet Biomedical Instruments

5225-4 Verona Road, Madison, WI, USA 53711, 608/271-3333, TWX 910-286-2711. Sales and Service Offices Worldwide, Subsidiary Offices: Canada, France, Germany, Japan, Mexico, The Netherlands and United Kingdom.

**NOW —
it's the
Nicolet
Neurotrac!**

Nicolet
Electrophysiology
Yesterday. Today. Tomorrow.

Anesthesia and Analgesia

Contents

Volume 65, Number 11, November 1986

SCIENTIFIC ARTICLES

- | | | |
|--|---|------|
| The Effect of β -Adrenergic Blockade on the Cardiovascular Response to Diltiazem or Verapamil in Dogs | Kathleen B. Sullivan and Patricia A. Kapur | 1099 |
| Comparative Toxicity of Atracurium and Metocurine in Isolated Rat Hepatocytes | Vladimir Nigrovic, James E. Klaunig, Sarah L. Smith, Norman E. Schultz, and Aron Wajskol | 1107 |
| Preoperative Oral Fluids: Is a Five-hour Fast Justified Prior to Elective Surgery? | J. Roger Maltby, A. D. Sutherland, J. P. Sale, and E. A. Shaffer | 1112 |
| Isoflurane Decreases the Cortisol Response to Cardiopulmonary Bypass | Paolo Flezzani, Narda D. Croughwell, R. William McIntyre, and J. G. Reves | 1117 |
| Effects of Ketamine on Low Intensity Tactile Sensory Input Are Not Dependent upon a Spinal Site of Action | J. G. Collins | 1123 |
| Effects of Halothane and Decreased PO ₂ on High Energy Phosphate Levels Maintained by Isolated Rat Liver Mitochondria | Gerald L. Becker, David J. Miletich, and Ronald F. Albrecht | 1130 |
| Intermittent Positive Pressure Ventilation with either Positive End-Expiratory Pressure or High Frequency Jet Ventilation (HFJV), or HFJV Alone in Human Acute Respiratory Failure | J. F. Brichant, J. J. Rouby, and P. Viars | 1135 |
| Genetic Predisposition to Liver Damage after Halothane Anesthesia in Guinea Pigs | Christine A. Lunam, Michael J. Cousins, and Pauline de la M. Hall | 1143 |
| Morphine and Fentanyl Interactions with Thiopental in Relation to Movement Response to Noxious Stimulation | Igor Kissin, John O. Mason III, and Edwin L. Bradley Jr | 1149 |
| Pharmacokinetics and Placental Transfer of Intravenous and Epidural Alfentanil in Parturient Women | E. Gepts, L. Heytens, and F. Camu | 1155 |
| Constant Flow Ventilation in Anesthetized Patients: Efficacy and Safety | Peter H. Breen, J. Iasha Sznajder, Paulette Morrison, Don Hatch, Larry D. H. Wood, and Douglas B. Craig | 1161 |
| The In Vitro and In Vivo Effects of Isoflurane and Nitrous Oxide on Platelet Aggregation | Brent G. Fauss, James C. Meadows, Christine Y. Bruni, and G. D. Qureshi | 1170 |
| Tourniquet Pain: A Volunteer Study | Rene R. P. M. Hagenouw, Phillip O. Bridenbaugh, Jan van Egmond, and Roger Stuebing | 1175 |

SCIENTIFIC ARTICLES—continued

Addition of Glucose to Bupivacaine in Spinal Anesthesia Increases Incidence of Tourniquet Pain	<i>Phillip O. Bridenbaugh, Rene R. P. M. Hagenouw, Mathieu J. M. Gielen, and Håkan H. Edström</i>	1181
Effect of Short-term Smoking Halt on Carboxyhemoglobin Levels and P ₅₀ Values	<i>J. Reddy Kambam, Lily H. Chen, and Steve A. Hyman</i>	1186
Comparison of Propofol with Methohexital for Outpatient Anesthesia	<i>Van A. Doze, Lynn M. Westphal, and Paul F. White</i>	1189
Cerebral Arteriovenous Oxygen Content Difference during Barbiturate Therapy in Patients with Acute Brain Damage	<i>Atsuo Sari, Yasutoshi Matayoshi, Akitomo Yonei, Hiroko Ogasahara, Tadahiko Nonoue, Kimio Yokota, and Shigeki Yamashita</i>	1196

SPECIAL ARTICLE

Spinal Subarachnoid Hematoma after Lumbar Puncture and Heparinization: A Case Report, Review of the Literature, and Discussion of Anesthetic Implications	<i>Eddie L. Owens, Gregory W. Kasten, and Eugene A. Hessel II</i>	1201
---	---	------

REVIEW ARTICLE

The Infant and the Myoneural Junction	<i>Nishan G. Goudsouzian and Frank G. Standaert</i>	1208
---------------------------------------	---	------

CLINICAL REPORTS

Assessment of Sterility of Pulmonary Arterial Catheter Sheaths	<i>Michael J. Murray, Mark Wignes, and John C. McMichan</i>	1218
Difficulty Reversing Drug-induced Coma in a Patient with Sleep Apnea	<i>Stanley I. Samuels and Wendy Rabinov</i>	1222
Anesthetic Management of a Patient with Reactive Airway Disease for Carbon Dioxide Laser Debulking of a Laryngeal Tumor	<i>Chester North, Brian Marsh, and Carol A. Hirshman</i>	1225
Anesthetic Management of a Child with an Intratracheal Tumor	<i>John G. Goode, Ralph F. Wetmore, and Thomas P. Keon</i>	1227
High Frequency Positive Pressure Ventilation during General Anesthesia for Extracorporeal Shock Wave Lithotripsy	<i>Aziel Perel, Benjamin Hoffman, Dov Podeh, and Joseph T. Davidson</i>	1231
Postoperative Seizures after Isoflurane Anesthesia	<i>Janet L. Harrison</i>	1235
Refractory Bradycardia after Reversal of Muscle Relaxant in a Diabetic with Vagal Neuropathy	<i>Anastasios N. Triantafillou, Kentaro Tsueda, Jeffrey Berg, and T. Jeffery Wieman</i>	1237
The Successful Treatment of Dural Puncture Headache after Failed Epidural Blood Patch	<i>Curtis L. Baysinger, Emil J. Menk, Edward Harte, and Robert Middaugh</i>	1242

LETTERS TO THE EDITOR

RAM Testing in Obstetric Patients	<i>Robert H. Boretsky</i>	1245
In Response	<i>Adrien Van Zundert, Leo Vaes, Paul Van Der Aa, Agnes Van Der Donck, and Herman Meeuwis</i>	1245
Succinylcholine-triggered Masseter Spasm in a Patient with Trigeminal Nerve Palsy	<i>Anis Baraka, Musa Muallem, and Hoda Karam</i>	1245
Analgesic Potencies of Dezocine and Butophanol	<i>Maurice Lippman</i>	1246
In Response	<i>Frederick M. Galloway</i>	1246
Disposable Circuit Tubing Melted by Heated Humidifier	<i>David H. Sprague and Gerald A. Maccioli</i>	1247
Laboratory False-positive Hyperkalemia in a Patient with Cold Agglutinins	<i>James R. Hlavacek, Richard Restifo, David Stone, and David Cullen</i>	1247
Hypertensive Response to Dinoprost under Anesthesia	<i>James F. Mayhew</i>	1248
Monitoring Inspired Oxygen Concentrations in Nonrebreathing Systems	<i>Donald W. Claeys</i>	1248
Cushing's Contributions to Anesthesia: Two Comments	<i>Leroy D. Vandam and David A. E. Shephard</i>	1249
In Response	<i>Nicholas P. Hirsch and Gary B. Smith</i>	1251
Naloxone-Morphine Synergism	<i>Krishnaswami Ramabadran and Mylarrao Bansinath</i>	1252

BOOK REVIEWS

The Pharmacological Basis of Therapeutics (seventh edition). A. Goodman Gilman, L. S. Goodman, A. Gilman, eds.	<i>D. Ryan Cook</i>	1253
The Heart: Physiology, Metabolism, Pharmacology, and Therapy. Lionel H. Opie.	<i>Carolyn J. Wilkinson</i>	1253
Primer of Water, Electrolyte and Acid-Base Syndromes. Emanuel Goldberger.	<i>Perry G. Fine</i>	1254
Intensive Care Medicine. J. M. Rippe, R. S. Irwin, J. S. Alpert, and J. E. Dalen, eds.	<i>Donald C. Finlayson</i>	1255
Anaesthetic Equipment: Physical Principles and Maintenance (second edition). C. S. Ward.	<i>Philip T. Conroi</i>	1255
Erratum		1256

PATIENT	O.R.	SERVICE	TIME
O'Leary	1	CV	7:45
oskowitz	2	CV	7:30
Leunings	3	CV	8:15
Traviotti	4	CV	7:45
Miller	5	GI	8:00
Foley	6	Gen	9:00

SUFENTA®

(sufentanil citrate) Injection



anesthesia for longer, more stressful procedures

Available in 1 ml, 2 ml, 5 ml ampoules; boxes of ten

Before prescribing, please consult complete prescribing information, of which the following is a brief summary.

CAUTION: Federal Law Prohibits Dispensing Without Prescription.

DESCRIPTION: SUFENTA is a sterile, preservative free, aqueous solution containing sufentanil citrate equivalent to 50 µg per ml of sufentanil base for intravenous injection. The solution has a pH range of 3.5-6.0.

INDICATIONS AND USAGE: SUFENTA (sufentanil citrate) is indicated: As an analgesic adjunct in the maintenance of balanced general anesthesia. As a primary anesthetic agent for the induction and maintenance of anesthesia with 100% oxygen in patients undergoing major surgical procedures, such as cardiovascular surgery or neurosurgical procedures in the sitting position, to provide favorable myocardial and cerebral oxygen balance or when extended postoperative ventilation is anticipated. SEE DOSAGE CHART FOR MORE COMPLETE INFORMATION ON THE USE OF SUFENTA.

CONTRAINDICATIONS: SUFENTA is contraindicated in patients with known hypersensitivity to the drug.

WARNINGS: SUFENTA should be administered only by persons specifically trained in the use of intravenous anesthetics and management of the respiratory effects of potent opioids.

An opioid antagonist, resuscitative and intubation equipment and oxygen should be readily available.

SUFENTA may cause skeletal muscle rigidity, particularly of the truncal muscles. The incidence and severity of muscle rigidity is dose related. Administration of SUFENTA may produce muscular rigidity with a more rapid onset than that seen with fentanyl. SUFENTA may produce muscular rigidity that involves the skeletal muscles of the neck and extremities. The incidence can be reduced by: 1) administration of up to 1/4 of the full paralyzing dose of a non-depolarizing neuromuscular blocking agent just prior to administration of SUFENTA at dosages of up to 8 µg/kg, 2) administration of a full paralyzing dose of a neuromuscular blocking agent following loss of consciousness when SUFENTA is used in anesthetic dosages (above 8 µg/kg) titrated by slow intravenous infusion, or, 3) simultaneous administration of SUFENTA and a full paralyzing dose of a neuromuscular blocking agent when SUFENTA is used in rapidly administered anesthetic dosages (above 8 µg/kg). The neuromuscular blocking agent should be compatible with the patient's cardiovascular status. Adequate facilities should be available for postoperative monitoring and

ventilation of patients administered SUFENTA. It is essential that these facilities be fully equipped to handle all degrees of respiratory depression.

PRECAUTIONS: General: The initial dose of SUFENTA should be appropriately reduced in elderly and debilitated patients. The effect of the initial dose should be considered in determining supplemental doses. Vital signs should be monitored routinely. Nitrous oxide may produce cardiovascular depression when given with high doses of SUFENTA (see CLINICAL PHARMACOLOGY). The hemodynamic effects of a particular muscle relaxant and the degree of skeletal muscle relaxation required should be considered in the selection of a neuromuscular blocking agent. High doses of pancuronium may produce increases in heart rate during SUFENTA-oxygen anesthesia. Bradycardia has been reported infrequently with SUFENTA-oxygen anesthesia and has been responsive to atropine. Respiratory depression caused by opioid analgesics can be reversed by opioid antagonists such as naloxone. Because the duration of respiratory depression produced by SUFENTA may last longer than the duration of the opioid antagonist action, appropriate surveillance should be maintained. As with all potent opioids, profound analgesia is accompanied by respiratory depression and diminished sensitivity to CO₂ stimulation which may persist into or recur in the postoperative period. Appropriate postoperative monitoring should be employed to ensure that adequate spontaneous breathing is established and maintained prior to discharging the patient from the recovery area. Interaction with Other Central Nervous System Depressants: Both the magnitude and duration of central nervous system and cardiovascular effects may be enhanced when SUFENTA is administered to patients receiving barbiturates, tranquilizers, other opioids, general anesthetics or other CNS depressants. In such cases of combined treatment, the dose of one or both agents should be reduced. Head Injuries: SUFENTA may obscure the clinical course of patients with head injuries. Impaired Respiration: SUFENTA should be used with caution in patients with pulmonary disease, decreased respiratory reserve or potentially compromised respiration. In such patients, opioids may additionally decrease respiratory drive and increase airway resistance. During anesthesia, this can be managed by assisted or controlled respiration. Impaired Hepatic or Renal Function: In patients with liver or kidney dysfunction, SUFENTA should be administered with caution due to the importance of these organs in the metabolism and excretion of SUFENTA.

Carcinogenesis, Mutagenesis and Impairment of Fertility: No long-term animal studies of SUFENTA have been performed to evaluate carcinogenic potential. The micronucleus test in female rats revealed that single intravenous

OPERATION	ANESTHESIOLOGIST	SURGEON
Coronary Bypass	Craig/Alvarez	Hodman
Intracranial Aneurysm	Lefcourt/Davies	D'Andrea
Total Hysterectomy	Sanford/Dewey	Higginson
LT. Total Hip Replacement	Connell/Schwartz	Bennett
Anterior Resection of Sigmoid Colon	Cohen/Rothman	Snyder
Thyroidectomy	Jane/Collins	Labitt

doses of SUFENTA as high as 80 µg/kg (approximately 2.5 times the upper human dose) produced no structural chromosome mutations. The Ames *Salmonella typhimurium* metabolic activating test also revealed no mutagenic activity. See ANIMAL TOXICOLOGY for reproduction studies in rats and rabbits.

Pregnancy Category C: SUFENTA has been shown to have an embryocidal effect in rats and rabbits when given in doses 2.5 times the upper human dose for a period of 10 days to over 30 days. These effects were most probably due to maternal toxicity (decreased food consumption with increased mortality) following prolonged administration of the drug. No evidence of teratogenic effects have been observed after administration of SUFENTA in rats or rabbits. There are no adequate and well-controlled studies in pregnant women. SUFENTA should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Labor and Delivery: There are insufficient data to support the use of SUFENTA in labor and delivery. Therefore, such use is not recommended.

Nursing Mothers: It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when SUFENTA is administered to a nursing woman.

Pediatric Use: The safety and efficacy of SUFENTA in children under two years of age undergoing cardiovascular surgery has been documented in a limited number of cases.

Animal Toxicology: The intravenous LD₅₀ of SUFENTA is 16.8 to 18.0 mg/kg in mice, 11.8 to 13.0 mg/kg in guinea pigs and 10.1 to 19.5 mg/kg in dogs. Reproduction studies performed in rats and rabbits given doses of up to 2.5 times the upper human dose for a period of 10 to over 30 days revealed high maternal mortality rates due to decreased food consumption and anoxia, which preclude any meaningful interpretation of the results.

ADVERSE REACTIONS: The most common adverse reactions of opioids are respiratory depression and skeletal muscle rigidity. See CLINICAL PHARMACOLOGY, WARNINGS and PRECAUTIONS on the management of respiratory depression and skeletal muscle rigidity. The most frequent adverse reactions in clinical trials involving 320 patients administered SUFENTA were: hypotension (7%), hypertension (3%), chest wall rigidity (3%) and bradycardia (3%). Other adverse reactions with a reported incidence of less than 1% were: **Cardiovascular:** tachycardia, arrhythmia; **Gastrointestinal:** nausea, vomiting; **Respiratory:** apnea, postoperative respiratory depression, bronchospasm; **Dermatological:** itching, erythema; **Central Nervous System:** chills; **Miscellaneous:** intraoperative muscle movement.

DRUG ABUSE AND DEPENDENCE: SUFENTA (sufentanil citrate) is a Schedule II controlled drug substance that can produce drug dependence of the morphine type and therefore has the potential for being abused.

OVERDOSAGE: Overdosage would be manifested by an extension of the pharmacological actions of SUFENTA (see CLINICAL PHARMACOLOGY) as with other potent opioid analgesics. However, no experiences of overdosage with SUFENTA have been established during clinical trials. The intravenous LD₅₀ of SUFENTA in male rats is 9.34 to 12.5 mg/kg (see ANIMAL TOXICOLOGY for LD₅₀s in other species). Intravenous administration of an opioid antagonist such as naloxone should be employed as a specific antidote to manage respiratory depression. The duration of respiratory depression following overdosage with SUFENTA may be longer than the duration of action of the opioid antagonist. Administration of an opioid antagonist should not preclude more immediate countermeasures. In the event of overdosage, oxygen should be administered and ventilation assisted or controlled as indicated for hypoventilation or apnea. A patent airway must be maintained, and a nasopharyngeal airway or endotracheal tube may be indicated. If depressed respiration is associated with muscular rigidity, a neuromuscular blocking agent may be required to facilitate assisted or controlled respiration. Intravenous fluids and vasopressors for the treatment of hypotension and other supportive measures may be employed.

DOSEAGE AND ADMINISTRATION: The dosage of SUFENTA should be individualized in each case according to body weight, physical status, underlying pathological condition, use of other drugs, and type of surgical procedure and anesthesia. In obese patients (more than 20% above ideal total body weight), the dosage of SUFENTA should be determined on the basis of lean body weight. Dosage should be reduced in elderly and debilitated patients (see PRECAUTIONS).

world leader in anesthesia research



JANSSEN
PHARMACEUTICA

Janssen Pharmaceutica Inc.
Piscataway, NJ 08854

© Janssen Pharmaceutica Inc. 1986

U.S. Patent No. 3,958,834
7618504-M
January 1986, March 1986

JPI-698

INTERNATIONAL ANESTHESIA RESEARCH SOCIETY THE B.B. SANKEY ANESTHESIA ADVANCEMENT AWARD

1986 AWARDS

The Board of Trustees of the IARS is pleased to advise that four Awards were granted and announced at the March 1986 meeting in Las Vegas, as follows:

Zeljko J. Bosnjak, PhD, Medical College of Wisconsin, Milwaukee, WI:

"Effects of Chronic Administration of Calcium Antagonists"

John F. Butterworth IV, MD, Bowman Gray School of Medicine, Winston-Salem, NC:

"Brain Cellular Mechanisms of Increased Anesthetic Susceptibility with Aging"

Philippe R. Housmans, MD, PhD, Mayo Foundation, Rochester, MN:

"Influence of Halothane on Intracellular Calcium Handling in Mammalian Cardiac Muscle"

Vladimir Nigrovic, MD, Medical College of Ohio, Toledo, OH:

"Adverse Reactions and Metabolism of Atracurium"

1987 B.B. SANKEY ANESTHESIA ADVANCEMENT AWARD

Applications for up to \$25,000 are invited for the 1987 Award, subject to the following basic conditions:

- The proposal must be within the general field of anesthesiology and may be for research, clinical care, education, or administration.
- The applicant must be a member of the International Anesthesia Research Society.
- Applications must be received in the IARS Cleveland office no later than December 15, 1986.
- The official application for the Award must be used. This form, as well as the guidelines for applicants, is available on request to:

International Anesthesia Research Society

3645 Warrensville Center Rd.

Cleveland, OH 44122

Telephone: (216) 295-1124

The 1987 Award(s) will be announced at the Annual Scientific Meeting (61st Congress) of the International Anesthesia Research Society to be held at the Buena Vista Palace, Lake Buena Vista (Orlando), Florida, March 14-18, 1987.

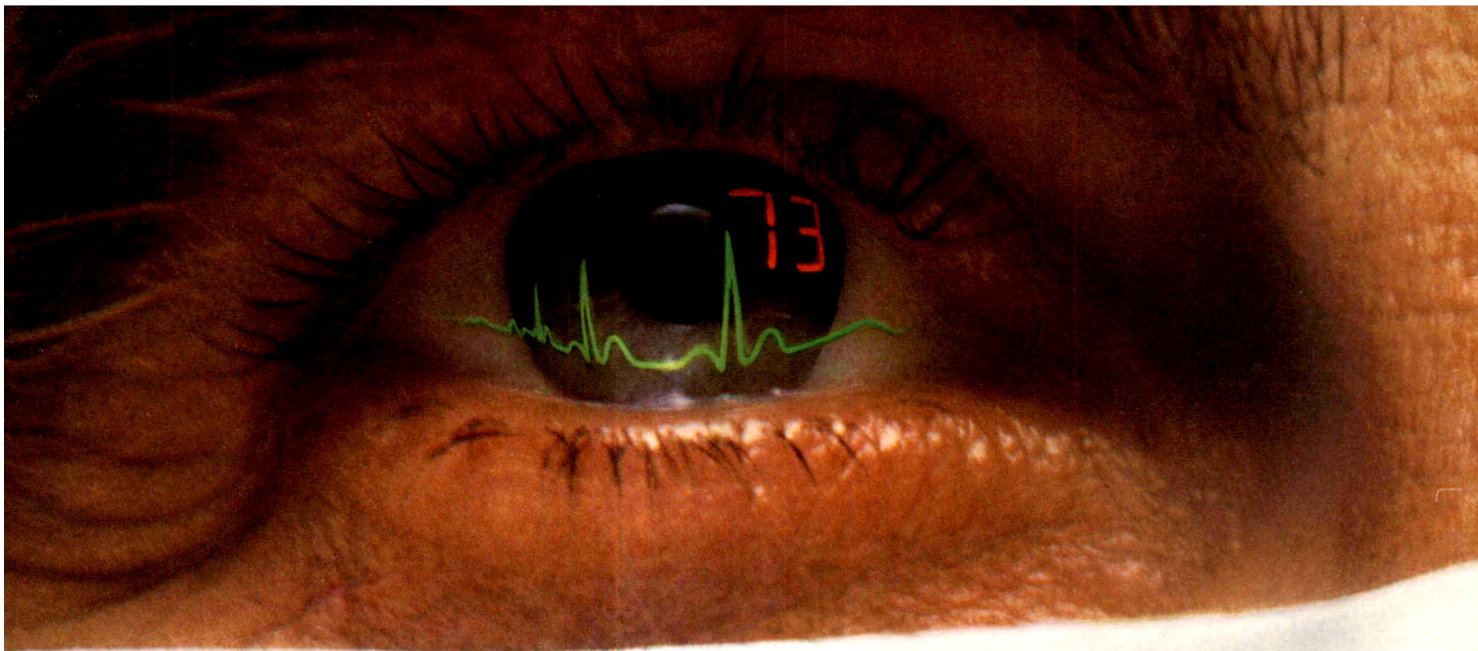




See for yourself.

**The only surgical muscle relaxant
free of clinically significant
cardiovascular and histamine-
related side effects...**

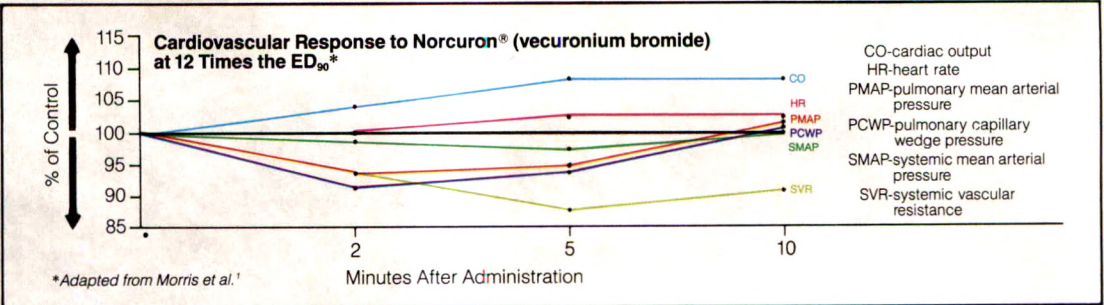
**ideal for your patients, including
those at risk.¹⁻⁵**



See the safety for yourself.

Free of clinically significant cardiovascular effects.*

NORCURON® is the only surgical muscle relaxant for which no clinically significant cardiovascular effects were observed in clinical trials.¹⁻⁴ In fact, even at 12 times effective doses, under halothane anesthesia,¹ NORCURON® produced no tachycardia, hypotension, or abnormalities of cardiodynamic function.

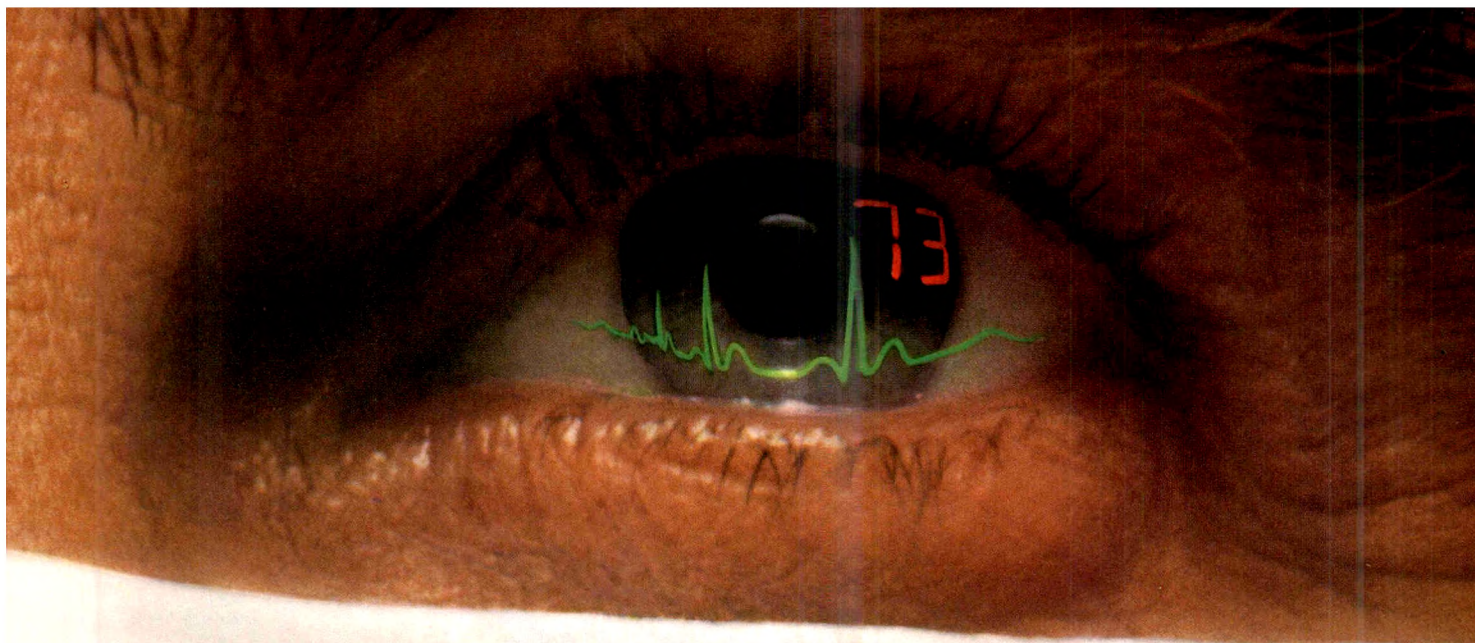


Histamine release or histamine-related side effects unlikely to occur...even at 3.5 times the ED₉₅.⁵

NORCURON® has not been shown to significantly affect circulating histamine, mean arterial blood pressure, and heart rate even in doses at the upper extreme of the recommended clinical range.⁵

The Effect of Nondepolarizing Muscle Relaxants*				Percent of Control		
Drug	Dose (mg/kg)	xED ₉₅	Histamine	Mean Arterial Pressure	Heart Rate	
Tubocurarine	0.5	1	410	78	116	
Metocurine	0.5†	2	212	79	119	
Atracurium	0.6†	3	192	80	108	
Vecuronium	0.1	1.7	117	100	99	
Vecuronium	0.2	3.5	87	99	102	

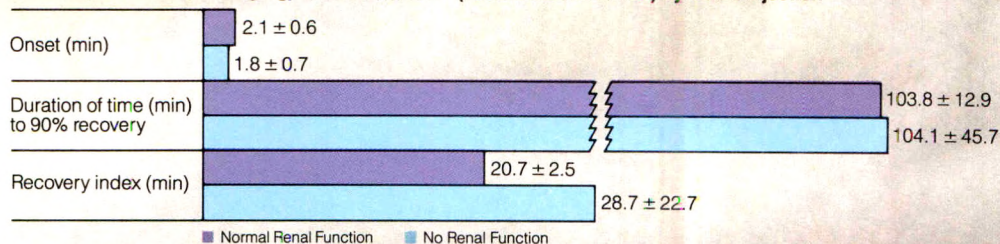
*Adapted from Basta et al.⁵
†0.1 mg/kg higher than recommended dose.



Performance unaffected by renal function.⁶

Despite administration of high doses of NORCURON®, no significant differences in onset time, duration of action, or recovery index have been noted between patients with and without renal function.⁶

Comparative Indices of Neuromuscular Blockade for Patients With and Without Renal Function Given Equal Doses (0.14 mg/kg)* of NORCURON® (vecuronium bromide) by Bolus Injection†



* Although high doses of NORCURON® were used to assess its pharmacokinetics, it is recommended that the initial dose not exceed 0.06 to 0.1 mg/kg.
† Adapted from Miller et al.⁶

**The surgical muscle relaxant
ideal for virtually all patients
including those at risk.**

Norcuron®

(vecuronium bromide) injection

See full prescribing information on following page.

References: 1. Morris RB, et al: The cardiovascular effects of vecuronium (ORG NC 45) and pancuronium in patients undergoing coronary artery bypass grafting. *Anesthesiology* 1983; 58:438-440. 2. Durant NN: Norcuron®—a new nondepolarizing neuromuscular blocking agent. *Semin Anesth* 1982; 1:47-56. 3. Krieg N, Crul JF, Booi LH: Relative potency of ORG NC 45, pancuronium, alcuronium, and tubocurarine in anesthetized man. *Br J Anaesth* 1980; 52:783-787. 4. Gallo JA, et al: Hemodynamic effects of bolus injection of

vecuronium in cardiac surgical patients. *Anesthesiology* 1984; 61:A63. 5. Basta SJ, et al: Vecuronium does not alter serum histamine within the clinical dose range. *Anesthesiology* 1983; 59:A273. 6. Miller RD, et al: Pharmacokinetics of vecuronium in patients with kidney disease, in Agoston S, et al (eds): *Clinical Experiences with Norcuron (ORG NC 45, Vecuronium Bromide)*. Amsterdam, Excerpta Medica, 1983, p 124.

Norcuron® (vecuronium bromide) injection

THIS DRUG SHOULD BE ADMINISTERED BY ADEQUATELY TRAINED INDIVIDUALS FAMILIAR WITH ITS ACTIONS, CHARACTERISTICS, AND HAZARDS.

DESCRIPTION: NORCURON® (vecuronium bromide) injection is a nondepolarizing neuromuscular blocking agent of intermediate duration, chemically designated as piperidinium, 1-[(2*B* 3*a*, 5*a*, 16*B*, 17*B*)-3, 17-bis(acetoxyloxy)-2-(1-piperidinyl)androstane-16-yl]-1-methyl-, bromide.

Norcuron® is supplied as a sterile nonpyrogenic freeze-dried buffer of very fine microscopic crystalline particles for intravenous injection only. Following reconstitution with solvent (water for injection) the resultant solution is isotonic and has a pH of 4. Each 5 ml vial contains 10 mg vecuronium bromide. Each vial also contains citric acid, dibasic sodium phosphate, sodium hydroxide, and/or phosphoric acid to buffer and adjust pH and mannitol to make isotonic. **CLINICAL PHARMACOLOGY:** Norcuron® (vecuronium bromide) injection is a nondepolarizing neuromuscular blocking agent possessing all of the characteristic pharmacological actions of this class of drugs (curariform). It acts by competing for cholinergic receptors at the motor end-plate. The antagonism to acetylcholine is inhibited and neuromuscular block is reversed by acetylcholinesterase inhibitors such as neostigmine, edrophonium, and pyridostigmine. Norcuron® is about 1/3 more potent than pancuronium; the duration of neuromuscular blockade produced by Norcuron® is shorter than that of pancuronium at initially equipotent doses. The time to onset of paralysis decreases and the duration of maximum effect increases with increasing Norcuron® doses. The use of a peripheral nerve stimulator is of benefit in assessing the degree of muscular relaxation.

The ED₅₀ (dose required to produce 50% suppression of the muscle twitch response with balanced anesthesia) has averaged 0.057 mg/kg (0.049 to 0.062 mg/kg in various studies). An initial Norcuron® dose of 0.08 to 0.10 mg/kg generally produces first depression of twitch in approximately 1 minute, good or excellent intubation conditions within 2.5 to 3.0 minutes, and maximum neuromuscular blockade within 3 to 5 minutes of injection in most patients. Under balanced anesthesia, the time to recovery to 25% of control (clinical facilitation) is approximately 25 to 40 minutes after injection and recovery is usually 95% complete approximately 45-65 minutes after injection of intubating dose. The neuromuscular blocking action of Norcuron® is slightly enhanced in the presence of potent inhalation anesthetics. If Norcuron® is first administered more than 5 minutes after the start of the inhalation of enflurane, isoflurane, or halothane, or when steady state has been achieved, the intubating dose of Norcuron® may be decreased by approximately 15% (see DOSAGE AND ADMINISTRATION section). Prior administration of succinylcholine may enhance the neuromuscular blocking effect of Norcuron® and its duration of action. With succinylcholine as the intubating agent, initial doses of 0.04-0.06 mg/kg of Norcuron® will produce complete neuromuscular block with clinical duration of action of 25-30 minutes. If succinylcholine is used prior to Norcuron®, the administration of Norcuron® should be delayed until the patient starts recovering from succinylcholine-induced neuromuscular blockade. The effect of prior use of other nondepolarizing neuromuscular blocking agents on the activity of Norcuron® has not been studied (see Drug Interactions).

Repeated administration of maintenance doses of Norcuron® has little or no cumulative effect on the duration of neuromuscular blockade. Therefore, repeat doses can be administered at relatively regular intervals with predictable results. After an initial dose of 0.08 to 0.10 mg/kg under balanced anesthesia, the first maintenance dose (suggested maintenance dose is 0.010 to 0.015 mg/kg) is generally required within 25 to 40 minutes; subsequent maintenance doses, if required, may be administered at approximately 12 to 15 minute intervals. Halothane anesthesia increases the clinical duration of the maintenance dose only slightly. Under enflurane a maintenance dose of 0.010 mg/kg is approximately equal to 0.015 mg/kg dose under balanced anesthesia.

The recovery index (time from 25% to 75% recovery) is approximately 15-25 minutes under balanced or halothane anesthesia. When recovery from Norcuron® neuromuscular blocking effect begins, it proceeds more rapidly than recovery from pancuronium. Once spontaneous recovery has started, the neuromuscular block produced by Norcuron® is readily reversed with various anticholinesterase agents, e.g. pyridostigmine, neostigmine, or edrophonium in conjunction with an anticholinergic agent such as atropine or glycopyrrolate. There have been no reports of recurarization following satisfactory reversal of Norcuron® induced neuromuscular blockade; rapid recovery is a finding consistent with its short elimination half-life.

Pharmacokinetics: At clinical doses of 0.04-0.10 mg/kg, 60-80% of Norcuron® is usually bound to plasma protein. The distribution half-life following a single intravenous dose (range 0.025-0.280 mg/kg) is approximately 4 minutes. Elimination half-life over this same dosage range is approximately 65-75 minutes in healthy surgical patients and in renal failure patients undergoing transplant surgery. In late pregnancy, elimination half-life may be shortened to approximately 35-40 minutes. The volume of distribution at steady state is approximately 300-400 ml/kg; systemic rate of clearance is approximately 3-4.5 ml/minute/kg. In man, urine recovery of Norcuron® varies from 3-35% within 24 hours. Data derived from patients requiring insertion of a T-tube in the common bile duct suggests that 25-50% of a total intravenous dose of vecuronium may be excreted in bile within 42 hours. Only unchanged Norcuron® (vecuronium bromide) injection has been detected in human plasma following clinical use. One metabolite, 3-deacetyl vecuronium, has been recovered in the urine of some patients in quantities that account for up to 10% of injected dose. 3-deacetyl vecuronium has also been recovered by T-tube in some patients accounting for up to 25% of the injected dose.

This metabolite has been judged by animal screening (dogs and cats) to have 50% or more of the potency of Norcuron®; equipotent doses are of approximately the same duration as Norcuron® in dogs and cats. Biliary excretion accounts for about half the dose of Norcuron® within 7 hours in the anesthetized rat. Circulatory bypass of the liver (cal preparation) prolongs recovery from Norcuron®. Limited data derived from patients with cirrhosis or cholestasis suggests that some measurements of recovery may be doubled in such patients. In patients with renal failure, measurements of recovery do not differ significantly from similar measurements in healthy patients.

Studies involving routine hemodynamic monitoring in good risk surgical patients reveal that the administration of Norcuron® in doses up to three times that needed to produce clinical relaxation (0.15 mg/kg) did not produce clinically significant changes in systolic, diastolic or mean arterial pressure. The heart rate, under similar monitoring, remained unchanged in some studies and was lowered by a mean of up to 8% in other studies. A large dose of 0.28 mg/kg administered during a period of no stimulation, while patients were being prepared for coronary artery bypass grafting, was not associated with alterations in rate-pressure-product or pulmonary capillary wedge pressure. Systemic vascular resistance was lowered slightly and cardiac output was increased insignificantly. The drug has not been studied in patients with hemodynamic dysfunction secondary to cardiac valvular disease. Limited clinical experience (3 patients) with use of Norcuron® during surgery for pheochromocytoma has shown that administration of this drug is not associated with changes in blood pressure or heart rate.

Unlike other nondepolarizing skeletal muscle relaxants, Norcuron® has no clinically significant effects on hemodynamic parameters and will not counteract those hemodynamic changes or known side effects produced by or associated with anesthetic agents.

Preliminary data on histamine assay in 16 patients and available clinical experience in more than 600 patients indicate that hypersensitivity reactions such as bronchospasm, flushing, redness, hypotension, tachycardia, and other reactions commonly associated with histamine release are unlikely to occur.

INDICATIONS AND USAGE: Norcuron® is indicated as an adjunct to general anesthesia, to facilitate endotracheal intubation and to provide skeletal muscle relaxation during surgery or mechanical ventilation.

CONTRAINDICATIONS: None known.

WARNINGS: NORCURON® SHOULD BE ADMINISTERED IN CAREFULLY ADJUSTED DOSAGE BY OR UNDER THE SUPERVISION OF EXPERIENCED CLINICIANS WHO ARE FAMILIAR WITH ITS ACTIONS AND THE POSSIBLE COMPLICATIONS THAT MIGHT OCCUR FOLLOWING ITS USE. THE DRUG SHOULD NOT BE ADMINISTERED UNLESS FACILITIES FOR INTUBATION, ARTIFICIAL RESPIRATION, OXYGEN THERAPY, AND REVERSAL AGENTS ARE IMMEDIATELY AVAILABLE. THE CLINICIAN MUST BE PREPARED TO ASSIST OR CONTROL RESPIRATION. In patients who are known to have myasthenia gravis or the myasthenic (Eaton-Lambert) syndrome, small doses of Norcuron® may have profound effects. In such patients, a peripheral nerve stimulator and use of a small test dose may be of value in monitoring the response to administration of muscle relaxants.

PRECAUTIONS: Renal Failure: Norcuron® is well-tolerated without clinically significant prolongation of neuromuscular blocking effect in patients with renal failure who have been optimally prepared for surgery by dialysis. Under emergency conditions in anephric patients some prolongation of neuromuscular blockade may occur, therefore, if anephric patients cannot be prepared for non-elective surgery, a lower initial dose of Norcuron® should be considered.

Altered Circulation Time: Conditions associated with slower circulation time in cardiovascular disease, old age, edematous states resulting in increased volume of distribution may contribute to a delay in onset time; therefore dosage should not be increased.

Hepatic Disease: Limited experience in patients with cirrhosis or cholestasis has revealed prolonged recovery time in keeping with the role the liver plays in Norcuron® metabolism and excretion (see Pharmacokinetics). Data currently available do not permit dosage recommendations in patients with impaired liver function.

UNDER THE ABOVE CONDITIONS, USE OF A PERIPHERAL NERVE STIMULATOR FOR ADEQUATE MONITORING OF NEUROMUSCULAR BLOCKING EFFECT WILL PRECLUDE INADVERTENT EXCESS DOSING.

Severe Obesity or Neuromuscular Disease: Patients with severe obesity or neuromuscular disease may pose airway and/or ventilatory problems requiring special care before, during and after the use of neuromuscular blocking agents such as Norcuron®.

Malignant Hyperthermia: Many drugs used in anesthetic practice are suspected of being capable of triggering a potentially fatal hypermetabolism of skeletal muscle known as malignant hyperthermia. There are insufficient data derived from screening in susceptible animals (swine) to establish whether or not Norcuron® is capable of triggering malignant hyperthermia.

Norcuron® has no known effect on consciousness, the pain threshold or cerebration. Administration must be accompanied by adequate anesthesia.

Drug Interactions: Prior administration of succinylcholine may enhance the neuromuscular blocking effect of Norcuron® (vecuronium bromide) injection and its duration of action. If succinylcholine is used before Norcuron®, the administration of Norcuron® should be delayed until the succinylcholine effect shows signs of wearing off. With succinylcholine as the intubating agent, initial doses of 0.04-0.06 mg/kg of Norcuron® may be administered to produce complete neuromuscular block with clinical duration of action of 25-30 minutes (see CLINICAL PHARMACOLOGY). The use of Norcuron® before succinylcholine, in order to attenuate some of the side effects of succinylcholine, has not been sufficiently studied.

Other nondepolarizing neuromuscular blocking agents (pancuronium, d-tubocurarine, metocurine, and gallamine) act in the same fashion as does Norcuron®, therefore these drugs and Norcuron® may manifest an additive effect when used together. There are insufficient data to support concomitant use of Norcuron® and other competitive muscle relaxants in the same patient.

Inhalational Anesthetics: Use of volatile inhalational anesthetics such as enflurane, isoflurane, and halothane with Norcuron® will enhance neuromuscular blockade. Potentiation is most prominent with use of enflurane and isoflurane. With the above agents the initial dose of Norcuron® may be the same as with balanced anesthesia unless the inhalational anesthetic has been administered for a sufficient time at a sufficient dose to have reached clinical equilibrium (see CLINICAL PHARMACOLOGY).

Antibiotics: Parenteral/intraperitoneal administration of high doses of certain antibiotics may intensify or produce neuromuscular block on their own. The following antibiotics have been associated with various degrees of paralysis: aminoglycosides (such as neomycin, streptomycin, kanamycin, gentamicin, and dihydrostreptomycin); tetracyclines; bacitracin; polymyxin B; colistin; and sodium colistimethate. These or other newly introduced antibiotics are used in conjunction with Norcuron® during surgery, unexpected prolongation of neuromuscular block should be considered a possibility. **Other:** Experience concerning injection of quinine during recovery from use of other muscle relaxants suggests that recurrent paralysis may occur. This possibility must also be considered for Norcuron®. Norcuron® induced neuromuscular blockade has been counteracted by alkalosis and enhanced by acidosis in experimental animals (cat). Electrolyte imbalance and diseases which lead to electrolyte imbalance, such as adrenal cortical insufficiency, have been shown to alter neuromuscular blockade. Depending on the nature of the imbalance, either enhancement or inhibition may be expected. Magnesium salts, administered for the management of toxemia of pregnancy, may enhance the neuromuscular blockade.

Drug/Laboratory Test Interactions: None known.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Long-term studies in animals have not been performed to evaluate carcinogenic or mutagenic potential or impairment of fertility.

Pregnancy: Pregnancy Category C: Animal reproduction studies have not been conducted with Norcuron®. It is also not known whether Norcuron® can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Norcuron® should be given to a pregnant woman only if clearly needed.

Pediatric Use: Infants under 1 year of age but older than 7 weeks, also tested under halothane anesthesia, are moderately more sensitive to Norcuron® on a mg/kg basis than adults and take about 1 1/2 times as long to recover. Information presently available does not permit recommendations for usage in neonates.

ADVERSE REACTIONS: Norcuron® was well-tolerated and produced no adverse reactions during extensive clinical trials. The most frequent adverse reaction to nondepolarizing blocking agents as a class consists of an extension of the drug's pharmacological action beyond the time period needed for surgery and anesthesia. This may vary from skeletal muscle weakness to profound and prolonged skeletal muscle paralysis resulting in respiratory insufficiency or apnea.

Inadequate reversal of the neuromuscular blockade, although not yet reported, is possible with Norcuron® as with all curariform drugs. These adverse reactions are managed by manual or mechanical ventilation until recovery is judged adequate. Little or no increase in intensity of blockade or duration of action of Norcuron® is noted from the use of thiobarbiturates, narcotic analgesics, nitrous oxide, or droperidol. See OVERDOSAGE for discussion of other drugs used in anesthetic practice which also cause respiratory depression.

OVERDOSAGE: There has been no experience with Norcuron® overdosage. The possibility of iatrogenic overdosage can be minimized by carefully monitoring muscle twitch response to peripheral nerve stimulation.

Excessive doses of Norcuron® can be expected to produce enhanced pharmacological effects. Residual neuromuscular blockade beyond the time period needed for surgery and anesthesia may occur with Norcuron® as with other neuromuscular blockers. This may be manifested by skeletal muscle weakness, decreased respiratory reserve, low tidal volume, or apnea. A peripheral nerve stimulator may be used to assess the degree of residual neuromuscular blockade and help to differentiate residual neuromuscular blockade from other causes of decreased respiratory reserve.

Respiratory depression may be due either wholly or in part to other drugs used during the conduct of general anesthesia such as narcotics, thiobarbiturates and other central nervous system depressants. Under such circumstances the primary treatment is maintenance of a patent airway and manual or mechanical ventilation until complete recovery of normal respiration is assured. Regonol® (pyridostigmine bromide injection), neostigmine, or edrophonium, in conjunction with atropine or glycopyrrolate will usually antagonize the skeletal muscle relaxant action of Norcuron®. Satisfactory reversal can be judged by adequacy of skeletal muscle tone and by adequacy of respiration. A peripheral nerve stimulator may also be used to monitor restoration of twitch height. Failure of prompt reversal (within 30 minutes) may occur in the presence of extreme debilitation, carcinomatosis, and with concomitant use of certain broad spectrum antibiotics, or anesthetic agents and other drugs which enhance neuromuscular blockade or cause respiratory depression of their own. Under such circumstances the management is the same as that of prolonged neuromuscular blockade. Ventilation must be supported by artificial means until the patient has resumed control of his respiration. Prior to the use of reversal agents, reference should be made to the specific package insert of the reversal agent.

DOSAGE AND ADMINISTRATION: Norcuron® (vecuronium bromide) injection is for intravenous use only. This drug should be administered by or under the supervision of experienced clinicians familiar with the use of neuromuscular blocking agents. Dosage must be individualized in each case. The dosage information which follows is derived from studies based upon units of drug per unit of body weight and is intended to serve as a guide only, especially regarding enhancement of neuromuscular blockade of Norcuron® by volatile anesthetics and by prior use of succinylcholine (see PRECAUTIONS/Drug Interactions). Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

To obtain maximum clinical benefits of Norcuron® and to minimize the possibility of overdosage, the monitoring of muscle twitch response to peripheral nerve stimulation is advised.

The recommended initial dose of Norcuron® is 0.08 to 0.10 mg/kg (1.4 to 1.75 times the ED₅₀) given as an intravenous bolus injection. This dose can be expected to produce good or excellent non-emergency intubation conditions in 2.5 to 3.0 minutes after injection. Under balanced anesthesia, clinically required neuromuscular blockade lasts approximately 25-30 minutes, with recovery to 25% of control achieved approximately 25 to 40 minutes after injection and recovery to 95% of control achieved approximately 45-65 minutes after injection. In the presence of potent inhalation anesthetics, the neuromuscular blocking effect of Norcuron® is enhanced. If Norcuron® is first administered more than 5 minutes after the start of inhalation agent or when steady state has been achieved, the initial Norcuron® dose may be reduced by approximately 15%, i.e., 0.060 to 0.085 mg/kg.

Prior administration of succinylcholine may enhance the neuromuscular blocking effect and duration of action of Norcuron®. If intubation is performed using succinylcholine, a reduction of initial dose of Norcuron® to 0.04-0.06 mg/kg with inhalation anesthesia and 0.05-0.06 mg/kg with balanced anesthesia may be required.

During prolonged surgical procedures, maintenance doses of 0.010 to 0.015 mg/kg of Norcuron® are recommended; after the initial Norcuron® injection, the first maintenance dose will generally be required within 25 to 40 minutes. However, clinical criteria should be used to determine the need for maintenance doses. Since Norcuron® lacks clinically important cumulative effects, subsequent maintenance doses, if required, may be administered at relatively regular intervals for each patient, ranging approximately from 12 to 15 minutes under balanced anesthesia, slightly longer under inhalation agents. (If less frequent administration is desired, higher maintenance doses may be administered.)

Should there be reason for the selection of larger doses in individual patients, initial doses ranging from 0.15 mg/kg up to 0.28 mg/kg have been administered during surgery under halothane anesthesia without ill effects to the cardiovascular system being noted as long as ventilation is properly maintained (see CLINICAL PHARMACOLOGY).

Dosage in Children: Older children (10 to 17 years of age) have approximately the same dosage requirements (mg/kg) as adults and may be managed the same way. Younger children (1 to 10 years of age) may require a slightly higher initial dose and may also require supplementation slightly more often than adults. Infants under one year of age but older than 7 weeks are moderately more sensitive to Norcuron® on a mg/kg basis than adults and take about 1 1/2 times as long to recover. See also subsection of PRECAUTIONS titled Pediatric Use. Information presently available does not permit recommendation on usage in neonates (see PRECAUTIONS).

COMPATIBILITY: Norcuron® is compatible in solution with:

0.9% NaCl solution

5% glucose in water

5% glucose in saline

Lactated Ringer's

HOW SUPPLIED: 5 ml vials (contains 10 mg of active ingredient) and 5 ml ampul of preservative-free sterile water for injection as the diluent. Boxes of 10 (NDC #0052-0442-17).

5 ml vials (contains 10 mg of active ingredient) only. DILUENT (Sterile Water for Injection, USP) NOT SUPPLIED. Boxes of 10 (NDC #0052-0442-57).

STORAGE: PROTECT FROM LIGHT. Store at 15°-30°C (59°-86°F).

AFTER RECONSTITUTION: Solution may be stored in refrigerator or kept at room temperature not to exceed 30°C (86°F). DISCARD SOLUTION AFTER 24 HOURS. DISCARD UNUSED PORTION. SINGLE USE VIALS.

Manufactured for ORGANON INC. by BEN VENUE LABORATORIES, INC. Bedford, OH 44146

ISSUED 5/86



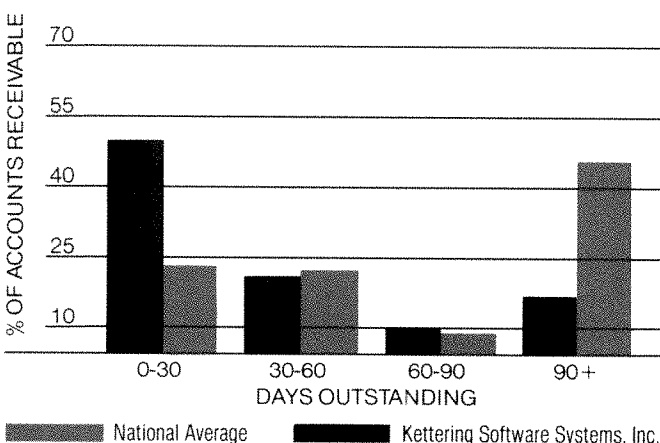
ORGANON INC
WEST ORANGE, NEW JERSEY 07052

Before you buy any Anesthesia Software Package read this:

The Kettering Anesthesia Software Package (ASP) will put you in control of your accounts...and control of your accounts is the most effective way to maintain close to 100% collection percentage. The Kettering Software ASP System is a billing system designed specifically for the anesthesiologist by a team of anesthesiologists and computer programmers.

Ask yourself if your practice is collection healthy...with a 93% collection rate or better...Kettering Software installations are helping group practices around the country manage their practice better and improve their collection efforts up to better than 93% of billings.

Account control is the key to the Kettering System.



The Kettering System gives control over an individual account from its entry into the system through claims processing and patient inquiry, right down to the pre-collection notification. The system automatically calculates the anesthesia charge based on time, modifiers, and the basic unit value of the procedure. This information is combined with the patient demographics to generate either a standard AMA claim form or to initiate an electronic transmittal to selected insurance carriers. After initial payment has been received, ASP will

automatically balance bill the secondary insurance if applicable. The quality that sets this system apart from the rest is account control and the guarantee that you can maximize your cash flow.

Kettering Systems Software people are ASA key contacts, always working to keep the ASP system ahead of the industry and its needs, and talking with legislators regularly about government actions to further the causes of the professional anesthesiologist. Want more information? Use the coupon for descriptive literature or write or call us today. We promise fast action.

Name _____
Address _____
City _____ State _____ Zip _____
Phone _____ Best Time? _____



KETTERING SOFTWARE SYSTEMS, INC.

2773 Orchard Run Road
Dayton, Ohio 45449
(513) 435-6135 1-800-221-5584

Specializing in Anesthesia Practice Management

Narkomed
3...

**unparalleled
power
and
performance**



Narkomed 3 is a new system combining the most reliable **basic anesthesia delivery instrument** with the most powerful and unique **information and monitoring capability** available anywhere. From the instant you energize the system... with a single switch... your control of Narkomed 3 can be classified as a breakthrough experience.

What's new about the patient-data displays?

Everything you see on this unique integrated and prioritized data-display screen is new. This is a sampling.

- Central Alarm Display, a tabulation in Warning, Caution, and Advisory format.
- Bargraph display of five important measurements for instant qualitative assessment.
- Central display for quantitative anesthesia documentation, with optional hardcopy presentation.
- Waveform display of respiratory measurements.
- Trending display of all anesthesia monitoring system measurements.

What is monitored by the Narkomed 3?

Six integrated monitors are available, from a total of eight, for display of patient-status data. Depending upon your choice, the information presented comprises...

- | | |
|--|--|
| <input type="checkbox"/> Oxygen Concentration | <input type="checkbox"/> Breathing Pressures |
| <input type="checkbox"/> Pulse Oximetry | <input type="checkbox"/> Carbon Dioxide |
| <input type="checkbox"/> Respiratory Volumes | <input type="checkbox"/> Blood Pressures |
| <input type="checkbox"/> Anesthesia Concentrations | <input type="checkbox"/> Temperatures |

The first two monitoring sources are standard. The other six monitors are optional. With an optional interface, certain other external monitors can be added.

Why hasn't there been a system like this before?

Because the variety of monitors now available were introduced, by many different makers, over a period of more than ten years. Often, the information they provided was not used because it was not controlled, integrated, or prioritized. Now, the unique Narkomed 3 puts you in full control of the system, with less effort. Experience it now. Contact your NAD Dealer, or call us directly.



NORTH
AMERICAN
DRÄGER

148B Quarry Road
Telford, Pennsylvania 18969
(215) 723-9824
or 248-0834
TWX 510-661-6148
NOAMDRAGER TEL

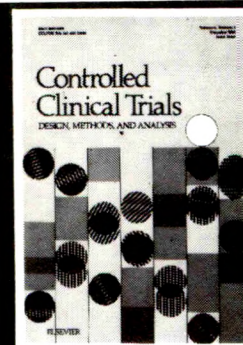


*The recognized authority on mounting
and evaluating clinical trials*

Controlled Clinical Trials

Design, Methods, and Analysis

Official Journal of the Society for Clinical Trials



Editor-in-Chief

Curtis L. Meinert

Department of Epidemiology
Johns Hopkins School of Hygiene and Public Health
Baltimore, Maryland

Associate Editors

Niels Tygstrup

Rigshospitalet
Copenhagen, Denmark

O. Dale Williams

University of North Carolina
Chapel Hill, North Carolina

Controlled Clinical Trials is a respected and valuable source of information for clinicians and statisticians involved in mounting and monitoring clinical trials and long-term follow-up studies. Its articles focus on design features or organizational structures that have contributed to the success of other studies — from short-term, small-scale trials to long-term multicenter investigations — and can be beneficially applied to similar projects.

Controlled Clinical Trials offers proven methods for:

- calculating sample size for long-term trials
- determining patient compliance in ongoing trials

- monitoring clinical trials for adverse or beneficial effects
- assessing costs

Recognizing the importance of effective data management, **Controlled Clinical Trials** features articles on the critical design and operating components of data processing systems that are used for maintaining a long-term data base, and quality assurance methods for error detection in data generation and processing procedures.

1986 Subscription Information

Volume 7 (4 issues)

Institutional Rate: \$112.00

Personal Rate: \$56.00

For air delivery in the U.S., Canada, or Mexico, add \$17.00. Subscribers outside the U.S. should add \$12.00 for surface delivery (not available to Europe); \$11.00 for surface air lift delivery to Europe; \$16.00 for surface air-lift delivery to Japan; or \$38.00 for air delivery to the rest of the world.

Sample copies are available upon request.
ISSN 0197-2456

Controlled Clinical Trials is abstracted/indexed in: Biological Abstracts, Current Contents/Life Sciences, Excerpta Medica, and Index Medicus.

For sample copies, send to

In North and South America:

Elsevier Science Publishing Co., Inc.
P.O. Box 1663
Grand Central Station
New York, NY 10163-1663

in the rest of the world:

Elsevier Science Publishers
Direct Mail Department
P.O. Box 211
1000 AE Amsterdam
The Netherlands

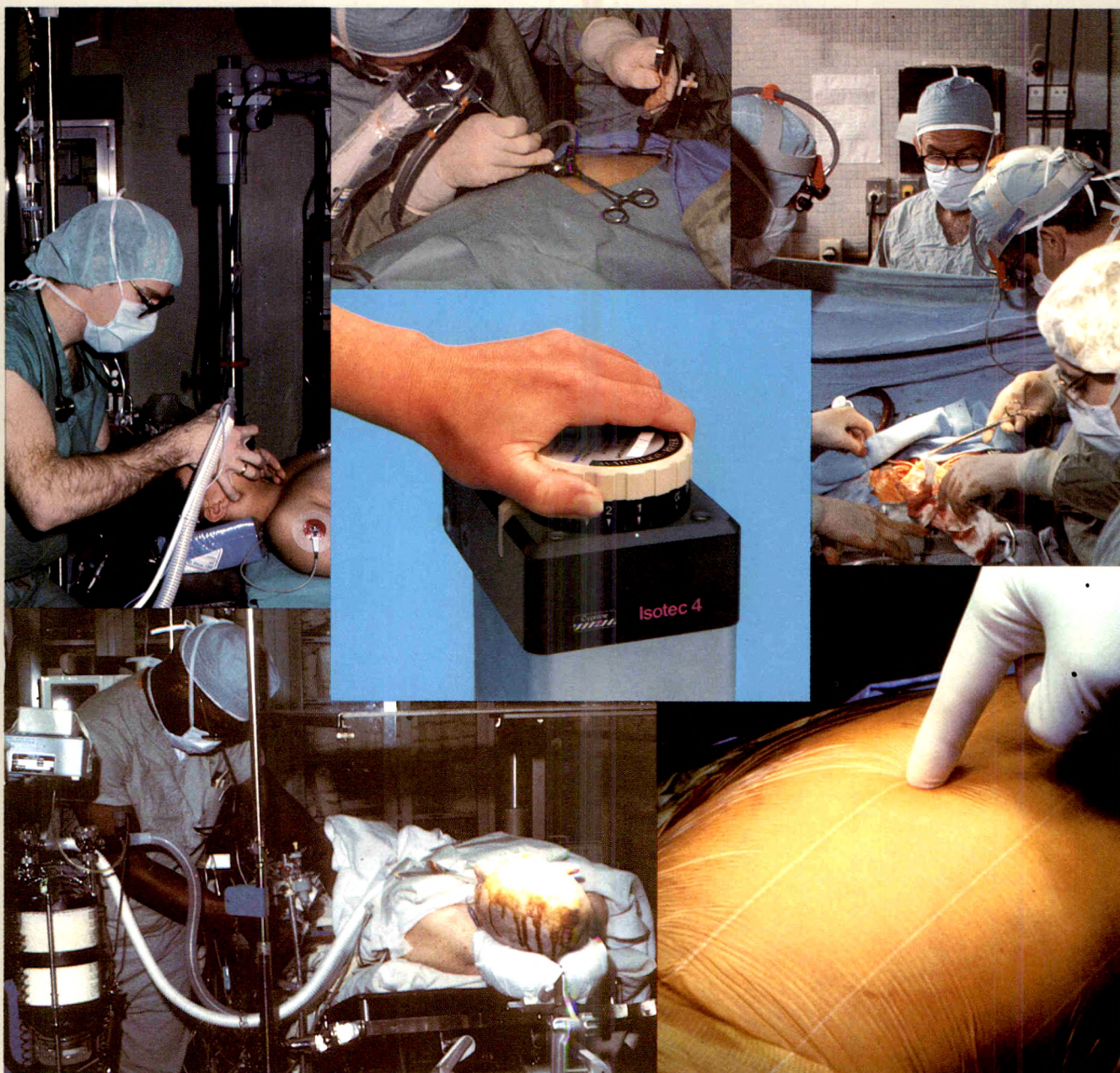
Note: Send subscription orders to either your usual supplier or the New York address. All subscriptions begin with the first issue of the calendar year and are entered upon receipt of payment. Subscription rates valid until December 31, 1986.

EB 365

Elsevier

Forane[®] (isoflurane)

The Versatile Anesthetic



Anaquest

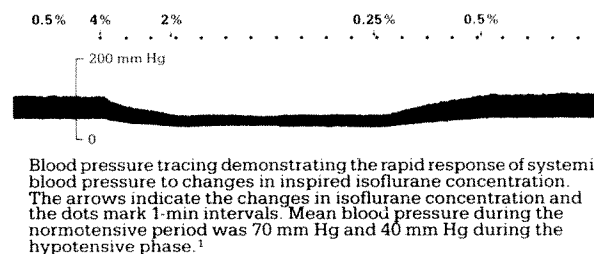
Forane[®] (isoflurane)



Forane[®] (isoflurane) The Versatile Anesthetic

A hypotensive agent for craniotomy and clipping of aneurysms

Isoflurane may be used as both anesthetic and hypotensive agent, providing for precise control of blood pressure throughout procedures such as clipping of cerebral aneurysms.¹



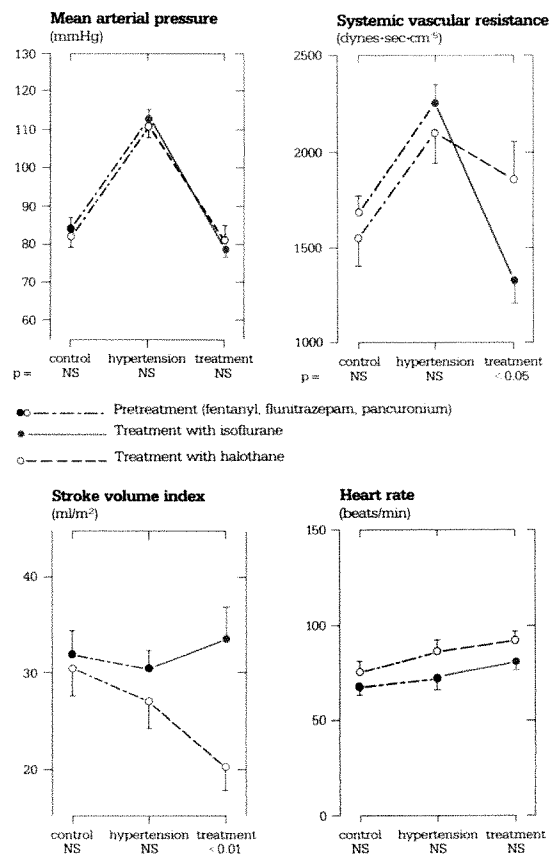
Control of intracranial pressure for craniotomy and excision of space-occupying lesion

Isoflurane causes no increase in intracranial pressure (ICP) when PaCO_2 is controlled at 25-30 torr, and ICP may be readily lowered during surgery by decreasing PaCO_2 .²

Control of hypertension during coronary artery bypass surgery

Control of intraoperative hypertension may be achieved with isoflurane by lowering peripheral vascular resistance (left ventricular afterload) generally without depressing stroke volume or increasing heart rate. These effects can be of particular benefit in patients with compromised left ventricular function. Halothane is equally effective in lowering blood pressure without increasing heart rate, but it decreases stroke volume.

Treatment of hypertension with either isoflurane or halothane anesthesia in patients undergoing coronary artery bypass surgery (Adapted from Hess et al³).



Potential of relaxants for orthopedic surgery

With isoflurane anesthesia, profound surgical muscle relaxation can be provided with one-third to two-thirds the usual relaxant dose (pancuronium, d-tubocurarine or atracurium).^{4,5} Thus the recovery period may be shortened and the need for reversal agents reduced by the rapid elimination of isoflurane.

Stability of heart rhythm when full hemostatic doses of epinephrine are needed

"Isoflurane, like enflurane, produces stable cardiac rhythm and, unlike halothane, does not sensitize the myocardium to the effects of catecholamines."⁶

A rapid recovery with few post-anesthetic symptoms for outpatient surgery

"Isoflurane is eliminated more rapidly than any other potent modern inhaled anesthetic."⁷ (Blood-gas partition coefficient, only 1.4)

Anesthesia using isoflurane in a mixture of oxygen and air produced a significantly lower incidence of nausea and vomiting following outpatient laparoscopy than anesthesia that included nitrous oxide.⁸

Post-laparoscopy Nausea (N) and Vomiting (V)		
Group	No. of Patients	No. of Patients with N or N&V
fentanyl, N ₂ O, O ₂	37	23 (62%)*
isoflurane, fentanyl, O ₂	20	6 (30%)
isoflurane, O ₂	20	5 (25%)

Adapted from Alexander et al⁸ *p<0.05

References:

1. Lam AM, Gelb AW: Cardiovascular effects of isoflurane-induced hypotension for cerebral aneurysm surgery. *Anesth Analg* 62:742-748, 1983.
2. Adams RW et al: Isoflurane and cerebrospinal fluid pressure in neurosurgical patients. *Anesthesiology* 54:97-99, 1981.
3. Hess W et al: Comparison of isoflurane and halothane when used to control intraoperative hypertension in patients undergoing coronary artery bypass surgery. *Anesth Analg* 62:15-20, 1983.
4. Miller RD et al: Comparative neuromuscular effects of pancuronium, gallamine, and succinylcholine during Forane and halothane anesthesia in man. *Anesthesiology* 35:509-514, 1971.
5. Tracrium® (atracurium besylate) prescribing information, Burroughs Wellcome Co., Research Triangle Park, NC 27709.
6. Wade JG, Stevens WC: Isoflurane: an anesthetic for the eighties? *Anesth Analg* 60(9):666-682, 1931.
7. Eger EI II: Isoflurane, a compendium and reference, Ohio Medical Anesthetics, Madison, WI, 1981.
8. Alexander GD et al: The role of nitrous oxide in postoperative nausea and vomiting. *Anesth Analg* 63:175, 1984.

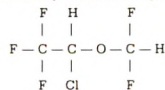
For complete use information, please see following page.

Forane® ...a product of original Anaquest research
(isoflurane)

Forane® ... The Versatile Anesthetic (isoflurane)

CAUTION: Federal Law Prohibits Dispensing without Prescription

DESCRIPTION: FORANE (isoflurane) is a nonflammable general inhalation anesthetic agent. It is 1-chloro-2,2,2-trifluoroethyl difluoromethyl ether, and its structural formula is:



Some physical constants are:

Molecular weight	184.5
Boiling point at 760 mm Hg	48.5 °C (uncorr.)
Refractive index n_D^{20}	1.2990-1.3005
Specific gravity 25 °/25 °C	1.496
Vapor pressure in mm Hg**	20 °C 238 25 °C 295 30 °C 367 35 °C 450

**Equation for vapor pressure calculation:

$$\log_{10} P_{\text{vap}} = A + \frac{B}{T} \quad \text{where:} \quad A = 8.056 \\ B = -1664.58 \\ T = ^\circ\text{C} + 273.16 \text{ (Kelvin)}$$

Partition coefficients at 37 °C

Water/gas	0.61
Blood/gas	1.43
Oil/gas	90.8

Partition coefficients at 25 °C - rubber and plastic

Conductive rubber/gas	62.0
Butyl rubber/gas	75.0
Polyvinyl chloride/gas	110.0
Polyethylene/gas	~2.0
Polyurethane/gas	~1.4
Polyolefin/gas	~1.1
Butyl acetate/gas	~2.5

Purity by gas chromatography

>99.9%

Lower limit of flammability in oxygen or nitrous oxide at 9 joules/sec. and 23 °C

None

Lower limit of flammability in oxygen or nitrous oxide at 900 joules/sec. and 23 °C

Greater than useful concentration in anesthesia

Isoflurane is a clear, colorless, stable liquid containing no additives or chemical stabilizers. Isoflurane has a mildly pungent, musty, ethereal odor. Samples stored in indirect sunlight in clear, colorless glass for five years, as well as samples directly exposed for 30 hours to a 2 amp, 115 volt, 60 cycle long wave UV light were unchanged in composition as determined by gas chromatography. Isoflurane in one normal sodium methoxide-methanol solution, a strong base, for over six months consumed essentially no alkali, indicative of strong base-stability. Isoflurane does not decompose in the presence of soda lime, and does not attack aluminum, tin, brass, iron or copper.

CLINICAL PHARMACOLOGY: FORANE (isoflurane) is an inhalation anesthetic. The MAC (minimum alveolar concentration) in man is as follows:

Age	100% Oxygen	70% N ₂ O
26 ± 4	1.28	0.56
44 ± 7	1.15	0.50
64 ± 5	1.05	0.37

Induction of and recovery from isoflurane anesthesia are rapid. Isoflurane has a mild pungency which limits the rate of induction, although excessive salivation or tracheobronchial secretions do not appear to be stimulated. Pharyngeal and laryngeal reflexes are readily abolished. The level of anesthesia may be changed rapidly with isoflurane. Isoflurane is a profound respiratory depressant. **RESPIRATION MUST BE MONITORED CLOSELY AND SUPPORTED WHEN NECESSARY.** As anesthetic dose is increased, tidal volume decreases and respiratory rates unchanged. This depression is partially reversed by surgical stimulation, even at deeper levels of anesthesia. Isoflurane evokes a high response reminiscent of that seen with diethyl ether and enflurane, although the frequency is less than with enflurane.

Blood pressure decreases with induction of anesthesia but returns toward normal with surgical stimulation. Progressive increases in depth of anesthesia produce corresponding decreases in blood pressure. Nitrous oxide diminishes the inspiratory concentration of isoflurane required to reach a desired level of anesthesia and may reduce the arterial hypotension seen with isoflurane alone. Heart rhythm is remarkably stable. With controlled ventilation and normal PaCO₂, cardiac output is maintained despite increasing depth of anesthesia primarily through an increase in heart rate which compensates for a reduction in stroke volume. The hypercapnia which attends spontaneous ventilation during isoflurane anesthesia further increases heart rate and raises cardiac output above awake levels. Isoflurane does not sensitize the myocardium to exogenously administered epinephrine in the dog. Limited data indicate that subcutaneous injection of 0.25 mg of epinephrine (50 mL of 1:200,000 solution) does not produce an increase in ventricular arrhythmias in patients anesthetized with isoflurane.

Muscle relaxation is often adequate for intra-abdominal operations at normal levels of anesthesia. Complete muscle paralysis can be attained with small doses of muscle relaxants. **ALL COMMONLY USED MUSCLE RELAXANTS ARE MARKEDLY POTENTIATED WITH ISOFLURANE. THE EFFECT BEING MOST PROFOUND WITH THE NONDEPOLARIZING TYPE.** Neostigmine reverses the effect of nondepolarizing muscle relaxants in the presence of isoflurane. All commonly used muscle relaxants are compatible with isoflurane.

Pharmacokinetics: Isoflurane undergoes minimal biotransformation in man. In the postanesthesia period, only 0.17% of the isoflurane taken up can be recovered as urinary metabolites.

INDICATIONS AND USAGE: FORANE (isoflurane) may be used for induction and maintenance of general anesthesia. Adequate data have not been developed to establish its application in obstetrical anesthesia.

CONTRAINDICATIONS: Known sensitivity to FORANE (isoflurane) or to other halogenated agents. Known or suspected genetic susceptibility to malignant hyperthermia.

WARNINGS: Since levels of anesthesia may be altered easily and rapidly, only vaporizers producing predictable concentrations should be used. Hypotension and respiratory depression increase as anesthesia is deepened.

Increased blood loss comparable to that seen with halothane has been observed in patients undergoing abortions.

FORANE (isoflurane) markedly increases cerebral blood flow at deeper levels of anesthesia. There may be a transient rise in cerebral spinal fluid pressure which is fully reversible with hyperventilation.

PRECAUTIONS: General: As with any potent general anesthetic, FORANE (isoflurane) should only be administered in an adequately equipped anesthetizing environment by those who are familiar with the pharmacology of the drug and qualified by training and experience to manage the anesthetized patient.

Information to Patients: Isoflurane, as well as other general anesthetics, may cause a slight decrease in intellectual function for 2 or 3 days following anesthesia. As with other anesthetics, small changes in moods and symptoms may persist for up to 6 days after administration.

Laboratory Tests: Transient increases in BSP retention, blood glucose and serum creatinine with decrease in BUN, serum cholesterol and alkaline phosphatase have been observed.

Drug Interactions: Isoflurane potentiates the muscle relaxant effect of all muscle relaxants, most notably nondepolarizing muscle relaxants, and MAC (minimum alveolar concentration) is reduced by concomitant administration of N₂O. See CLINICAL PHARMACOLOGY.

Carcinogenesis: Swiss ICR mice were given isoflurane to determine whether such exposure might induce neoplasia. Isoflurane was given at 1/2, 1/8 and 1/32 MAC for four in-utero exposures and for 24 exposures to the pups during the first nine weeks of life. The mice were killed at 15 months of age. The incidence of tumors in these mice was the same as in untreated control mice which were given the same background gases, but not the anesthetic.

Pregnancy Category C: Isoflurane has been shown to have a possible anesthetic-related fetotoxic effect in mice when given in doses 6 times the human dose. There are no adequate and well-controlled studies in pregnant women. Isoflurane should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers: It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when isoflurane is administered to a nursing woman.

Malignant Hyperthermia: In susceptible individuals, isoflurane anesthesia may trigger a skeletal muscle hypermetabolic state leading to high oxygen demand and the clinical syndrome known as malignant hyperthermia. The syndrome includes nonspecific features such as muscle rigidity, tachycardia, tachypnea, cyanosis, arrhythmias, and unstable blood pressure. (It should also be noted that many of these nonspecific signs may appear with light anesthesia, acute hypoxia, etc.) An increase in overall metabolism may be reflected in an elevated temperature (which may rise rapidly early or late in the case, but usually is not the first sign of augmented metabolism) and an increased usage of the CO₂ absorption system (hot canister). PaO₂ and pH may decrease, and hyperkalemia and a base deficit may appear. Treatment includes discontinuance of triggering agents (e.g., isoflurane), administration of intravenous dantrolene sodium, and application of supportive therapy. Such therapy includes vigorous efforts to restore body temperature to normal, respiratory and circulatory support as indicated, and management of electrolyte-fluid-acid-base derangements. (Consult prescribing information for dantrolene sodium intravenous for additional information on patient management.) Renal failure may appear later, and urine flow should be sustained if possible.

ADVERSE REACTIONS: Adverse reactions encountered in the administration of FORANE (isoflurane) are in general dose dependent extensions of pharmacophysiologic effects and include respiratory depression, hypotension and arrhythmias.

Shivering, nausea, vomiting and ileus have been observed in the postoperative period.

As with all other general anesthetics, transient elevations in white blood count have been observed even in the absence of surgical stress.

See PRECAUTIONS for information regarding malignant hyperthermia.

OVERDOSAGE: In the event of overdosage, or what may appear to be overdosage, the following action should be taken:

Stop drug administration, establish a clear airway and initiate assisted or controlled ventilation with pure oxygen.

DOSAGE AND ADMINISTRATION: Premedication: Premedication should be selected according to the need of the individual patient, taking into account that secretions are weakly stimulated by FORANE (isoflurane) and the heart rate tends to be increased. The use of anticholinergic drugs is a matter of choice.

Inspired Concentration: The concentration of isoflurane being delivered from a vaporizer during anesthesia should be known. This may be accomplished by using:

- vaporizers calibrated specifically for isoflurane;
- vaporizers from which delivered flows can be calculated, such as vaporizers delivering a saturated vapor which is then diluted. The delivered concentration from such a vaporizer may be calculated using the formula:

$$\% \text{ isoflurane} = \frac{100 P_V F_V}{F_T (P_A - P_V)}$$

where: P_A = Pressure of atmosphere
 P_V = Vapor pressure of isoflurane
 F_V = Flow of gas through vaporizer (mL/min)
 F_T = Total gas flow (mL/min)

Isoflurane contains no stabilizer. Nothing in the agent alters calibration or operation of these vaporizers.

Induction: Induction with isoflurane in oxygen or in combination with oxygen-nitrous oxide mixtures may produce coughing, breath holding, or laryngospasm. These difficulties may be avoided by the use of a hypnotic dose of an ultra-short-acting barbiturate. Inspired concentrations of 1.5 to 3.0% isoflurane usually produce surgical anesthesia in 7 to 10 minutes.

Maintenance: Surgical levels of anesthesia may be sustained with a 1.0 to 2.5% concentration when nitrous oxide is used concomitantly. An additional 0.5 to 1.0% may be required when isoflurane is given using oxygen alone. If added relaxation is required, supplemental doses of muscle relaxants may be used.

The level of blood pressure during maintenance is an inverse function of isoflurane concentration in the absence of other complicating problems. Excessive decreases may be due to depth of anesthesia and in such instances may be corrected by lightening anesthesia.

HOW SUPPLIED: FORANE (isoflurane), NDC 10019-360-40, is packaged in 100 mL amber-colored bottles.

Storage: Store at room temperature. Isoflurane contains no additives and has been demonstrated to be stable at room temperature for periods in excess of five years.

A-0117

Revised 5-84

Anaquest Forane® (isoflurane)

Anaquest
2005 West Beltline Highway
Madison WI 53713 2318
608 273 0019
Telex 910 286 2792
A Division of BOC Inc





Specify
Quality
of Life...
Simply
& Cost-
Effectively.

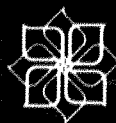
Specify CORMED II™ Ambulatory Infusion System

CORMED II Ambulatory Infusion Pump provides therapeutic flexibility & simplicity for you and your patients. CORMED II...no complicated keyboard data entry...no cassettes...no cumbersome multiple connections...and no excess bulk. For you, there's proven pump technology, and freedom to administer precise continuous infusions up to 5 days without battery change. For your patients, there are audible/visual alarms & a constant flow rate display. Plus the convenience & security of an easy-to-use external pump.

CORMED II. A sound response to today's healthcare environment that can measurably improve your patient's quality of life.

- ▲ **Supports wide range of therapies**—6-50ml/day flow range (adjustable in 0.1 ml increments)
- ▲ **Added security**—60CC drug reservoir bag is protected inside pump case (larger volume external bag, optional).
- ▲ **Lower operating costs than disposable batteries**—Rechargeable snap-in 5-day battery
- ▲ **No expensive cassettes or additional tubing sets needed**—Low cost integrated bag & tubing set
- ▲ **Simple to operate**—The only controls are the on-off switch and the rate set knob.

A CORMED representative will be happy to discuss exactly how you may best utilize the CORMED II to help control your patient's pain.



CORMED Inc.™

World leader in outpatient ambulatory infusion systems

591 Mahar Street, Dept. AN8, Medina NY 14103
716-798-4900 • Telex: 501783

**Albumin & PPF
are no safer
or more
effective than
Hespan[®]
(hetastarch)**

...they're simply

As safe as albumin or PPF

In comparative clinical studies, platelet counts, hematocrits, serum fibrinogen levels, prothrombin times (PT), and partial thromboplastin times (PTT) seen with Hespan were comparable to those seen with albumin or plasma protein fraction (PPF).^{1,2}

Other studies demonstrate that when any reduction in platelet count or prolongation of PT or PTT does occur with Hespan, no increased bleeding results, even in patients with multiple trauma.³⁻⁵ As with any volume expander, patients should be monitored for excessive hemodilution of coagulant factors or circulatory overload when large volumes are administered.

When Hespan-treated patients were monitored to detect localized or

systemic sepsis, there was no evidence of a decrease in their ability to ward off infection or combat an established infection.⁵

Hespan is nonantigenic and, as with blood-derived colloids, any risk of allergic reaction is minimal. Hespan also has a negligible effect on subsequent blood typing or cross-matching.⁶

As effective as albumin or PPF

Comparative clinical studies have repeatedly demonstrated that Hespan is as effective as albumin or PPF in postoperative myocardial revascularization,¹⁻³ and hemorrhagic, traumatic, or septic shock.^{4,5,7}

No significant differences between Hespan and albumin or PPF were noted in any efficacy parameter.^{1-5,7}

Hespan effectively maintained colloid osmotic pressure, restored plasma volume, and improved cardiac output and renal function in hypovolemic patients.^{1-5,7} And, the volume-expanding effect of a single infusion of Hespan can persist for 24 hours or longer.

Half the price of albumin or PPF

Hespan offers a potential savings to your hospital of tens of thousands of dollars a year.

double the price.



For additional information, contact the Medical Services Department, American Critical Care, 1600 Waukegan Road, McGaw Park, IL 60085. Phone 1-800-323-4980.

Lifesaving,
moneysaving



HESPAN[®]
(hetastarch)



American Critical Care

American Hospital Supply Corporation

Please see references and brief summary of prescribing information on following page.

References: 1. Diehl JT, Lester JL, Cosgrove DM: Clinical comparison of hetastarch and albumin in postoperative cardiac patients. *Ann Thorac Surg* 34 (6):674-679, 1982. 2. Moggio RA, Rha CC, Somborg ED, et al: Hemodynamic comparison of albumin and hydroxyethyl starch in postoperative cardiac surgery patients. *Crit Care Med* 11 (12):943-945, 1983. 3. Kirilini JK, Lell WA, Kouchoykos NT: Hydroxyethyl starch versus albumin for colloid infusion following cardiopulmonary bypass in patients undergoing myocardial revascularization. *Ann Thorac Surg* 37 (1):40-46, 1984. 4. Puri VK, Pakdipaty B, White L: Hydroxyethyl starch for resuscitation of patients with hypovolemia and shock. *Crit Care Med* 9 (12):833-837, 1981. 5. Shatney CH, Deepika K, Militello PR, et al: Efficacy of hetastarch in the resuscitation of patients with multisystem trauma and shock. *Arch Surg* 118:804-809, 1983. 6. Daniels MJ, Strauss RG, Smith-Floss AM: Effects of hydroxyethyl starch on erythrocyte typing and blood crossmatching. *Transfusion* 22 (3):226-228, 1982. 7. Rackow EC, Falk JL, Fein IA, et al: Fluid resuscitation in circulatory shock: A comparison of the cardiorespiratory effects of albumin, hetastarch, and saline solutions in patients with hypovolemic and septic shock. *Crit Care Med* 11(11):839-850, 1983.

HESPAN[®] (hetastarch)

6% Hetastarch in 0.9% Sodium Chloride Injection

CONTRAINDICATIONS

Hetastarch is contraindicated in patients with severe bleeding disorders or with severe congestive cardiac and renal failure with oliguria or anuria.

WARNINGS

Large volumes may alter the coagulation mechanism. Thus, administration of hetastarch may result in transient prolongation of prothrombin, partial thromboplastin and clotting times. With administration of large doses, the physician should also be alert to the possibility of transient prolongation of bleeding time.

Hematocrit may be decreased and plasma proteins diluted excessively by administration of large volumes of hetastarch.

Usage in Leukapheresis: Significant declines in platelet counts and hemoglobin levels have been observed in donors undergoing repeated leukapheresis procedures due to the volume expanding effects of hetastarch. Hemoglobin levels usually return to normal within 24 hours. Hemodilution by hetastarch and saline may also result in 24 hour declines of total protein, albumin, calcium and fibrinogen values.

Usage in Pregnancy: Reproduction studies have been done in mice with no evidence of fetal damage. Relevance to humans is not known since hetastarch has not been given to pregnant women. Therefore, it should not be used in pregnant women, particularly during early pregnancy, unless in the judgment of the physician the potential benefits outweigh the potential hazards.

Usage in Children: No data available pertaining to use in children.

The safety and compatibility of additives have not been established.

PRECAUTIONS

The possibility of circulatory overload should be kept in mind. Special care should be exercised in patients who have impaired renal clearance, since this is the principal way in which hetastarch is eliminated. Caution should be used when the risk of pulmonary edema and/or congestive heart failure is increased. Indirect bilirubin levels of 0.83 mg% (normal 0.0-0.7 mg%) have been reported in 2 out of 20 normal subjects who received multiple hetastarch infusions. Total bilirubin was within normal limits at all times; indirect bilirubin returned to normal by 96 hours following the final infusion. The significance, if any, of these elevations is not known; however, caution should be observed before administering hetastarch to patients with a history of liver disease.

Regular and frequent clinical evaluation and laboratory determinations are necessary for proper monitoring of hetastarch use during leukapheresis. Studies should include CBC, total leukocyte and platelet counts, leukocyte differential count, hemoglobin, hematocrit, prothrombin time (PT), and partial thromboplastin time (PTT).

Hetastarch is nonantigenic. However, allergic or sensitivity reactions have been reported (see ADVERSE REACTIONS). If such reactions occur, they are readily controlled by discontinuation of the drug and, if necessary, administration of an antihistaminic agent.

ADVERSE REACTIONS

The following have been reported: vomiting, mild temperature elevation, chills, itching, submaxillary and parotid glandular enlargement, mild influenza-like symptoms, headaches, muscle pains, peripheral edema of the lower extremities, and anaphylactoid reactions consisting of periorbital edema, urticaria, and wheezing.

HOW SUPPLIED

NDC 0094-0037-05-Hespan[®] (6% Hetastarch in 0.9% Sodium Chloride Injection) is supplied sterile and nonpyrogenic in 500 ml intravenous infusion bottles.

CAUTION

Federal (U.S.A.) law prohibits dispensing without prescription.

Rev: Feb., 1982

Distributed by

American Critical Care



American Hospital Supply Corporation
McGaw Park, IL USA 60085



Now Published by Elsevier:

Journal of the American Geriatrics Society

GENE H. STOLLERMAN, MD
Editor
Boston University Hospitals
Boston, MA

JOHN P. BLASS, MD, PhD
Associate Editor
White Plains, NY

Journal of the American Geriatrics Society has been providing the medical community with outstanding original coverage of all aspects of geriatrics for over 30 years. Emphasizing original research, *Journal of the American Geriatrics Society* publishes both clinical and basic science studies on a broad range of topics. A distinguished editorial board, drawn from a wide variety of medical specialties, ensures the accuracy, high quality, and newsworthiness of every contribution selected for publication.

Regular features of *Journal of the American Geriatrics Society* include:

- **Medical Ethics and Humanities**
thought-provoking viewpoints on the difficult ethical questions facing all physicians who treat the elderly
- **Law and Public Policy**
clear, concise reports on the latest legislative and judicial developments that affect patient management
- **Clinical Experience**
practical solutions to common problems in geriatric health care

Geriatricians, internists, cardiologists, rheumatologists, psychiatrists, endocrinologists, family practitioners, and others who treat aging patients rely on *Journal of the American Geriatrics Society* for up-to-date information on all aspects of geriatric health care.

Journal of the American Geriatrics Society is abstracted/indexed in *Index Medicus*, *Current Contents*, *Science Citation Index*, *Automatic Subject Citation Alert*, *Social Sciences Citation Index*, and *ISI/BIOMED*.

1986 Subscription Information:

Journal of the American Geriatrics Society

Volume 34, 12 issues, 1986

Institutional Rate: \$75.00

Personal Rate: \$65.00

For air delivery in the U.S., Canada, and Mexico, add \$28.00. Subscribers outside the U.S. should add \$13.00 for surface delivery (not available to Europe); \$17.00 for surface air lift delivery to Europe; \$55.00 for air delivery to the rest of the world; \$29.00 for surface air-lift delivery to Japan.

Sample copies are available.

ISSN: 0002-8614

For sample copies, send to

In North and South America:
Elsevier Science Publishing Co., Inc.
P.O. Box 1663
Grand Central Station
New York, NY 10163-1663

In the rest of the world:
Elsevier Science Publishers
Direct Mail Department
P.O. Box 211
1000 AE Amsterdam
The Netherlands

Note: Send subscription orders to either your usual supplier or the New York address. All subscriptions begin with the first issue of the calendar year. Subscription rates valid through Dec. 31, 1986.

IARS MEMBERSHIP

FOR YOUR IN-TRAINING AND CONTINUING MEDICAL EDUCATION

The International Anesthesia Research Society is a non-profit, scientific and educational corporation of the State of Ohio, founded in 1922 "to foster progress and research in anesthesia." To this end the Society

Publishes the oldest journal in the specialty, *Anesthesia and Analgesia*

Sponsors an annual scientific meeting (Congress) which is held in March each year

Funds anesthesia-related research through the IARS B.B. Sankey Anesthesia Advancement Award

Membership in the IARS is voluntary; it is also separate and distinct from membership in any other local, state, regional or national anesthesia organization or association. Membership is open to individuals who qualify in the various categories shown below; who complete the appropriate application and submit it to the IARS Cleveland office with the applicable dues. All memberships include a subscription to *Anesthesia and Analgesia*. Members and Associate Members are entitled to a reduced registration fee at the IARS annual meeting; Educational Members pay no registration fee.

. . . . MEMBERSHIP CATEGORIES

MEMBERSHIP: Open to individuals with doctorate degrees, who are licensed to practice in the medical, osteopathic, dental or veterinary medicine fields (i.e., MD, MB, DO, DDS, DMD, DVM); and to individuals with doctorate degrees in any scientific discipline (PhD), who are engaged in academic, private or commercial research.

ASSOCIATE MEMBERSHIP: Open to individuals in the allied health professions, duly certified by their professional accrediting organization as nurse anesthetists (CRNA); respiratory therapists or technicians (RRT or CRTT); physician/anesthesia assistants (PA/MMS); and other allied health professionals in anesthesia-related practice.

Annual Dues for Members and Associate Members: \$50.00 U.S.; \$61.00 foreign.

These memberships are entered on a calendar year basis only.

EDUCATIONAL MEMBERSHIP: Open (with certification by program director) to doctors (interns/residents) enrolled in anesthesiology training programs; nurses enrolled in nurse anesthesia schools; students enrolled in programs leading to certification as physician assistants, respiratory therapists or technicians

Annual Dues for Educational Members: One-half of member rate. These memberships are entered in January or July for 2, 3, or 4 year periods. Applications, certified by program directors, must accompany check to cover full membership period.

International Anesthesia Research Society
3645 Warrensville Center Road, Cleveland, Ohio 44122, USA

Please send me _____ application(s) for: Membership (_____)
Associate Membership (_____)
Educational Membership (_____)

Please print clearly: _____
Name and Degree (MD, DO, CRNA, RN, RRT, etc.)

Street Address

City, State, Zip Code (country)

For every indication,



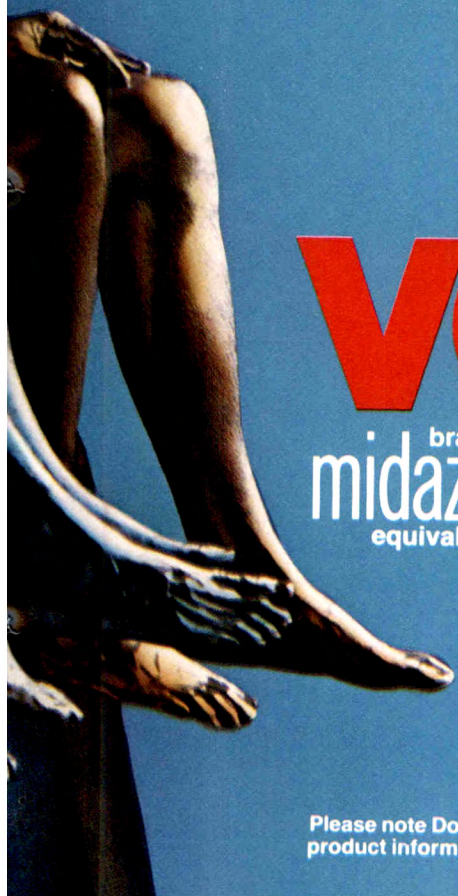
Artist's conception of the levels of sedation you can achieve with VERSED (midazolam HCl/Roche): 1) preoperative medication, 2) I.V. conscious sedation, 3) induction of anesthesia and as a component of balanced anesthesia.



Copyright © 1986 by Hoffmann-La Roche Inc. All rights reserved.

a particular advantage

- **Premedication:**
virtually painless on injection...
fast sedative and amnestic action¹
- **I.V. conscious sedation:**
superior amnestic effect...
less tissue irritation¹
- **Induction and as a component of balanced anesthesia:**
smooth induction... smooth emergence¹

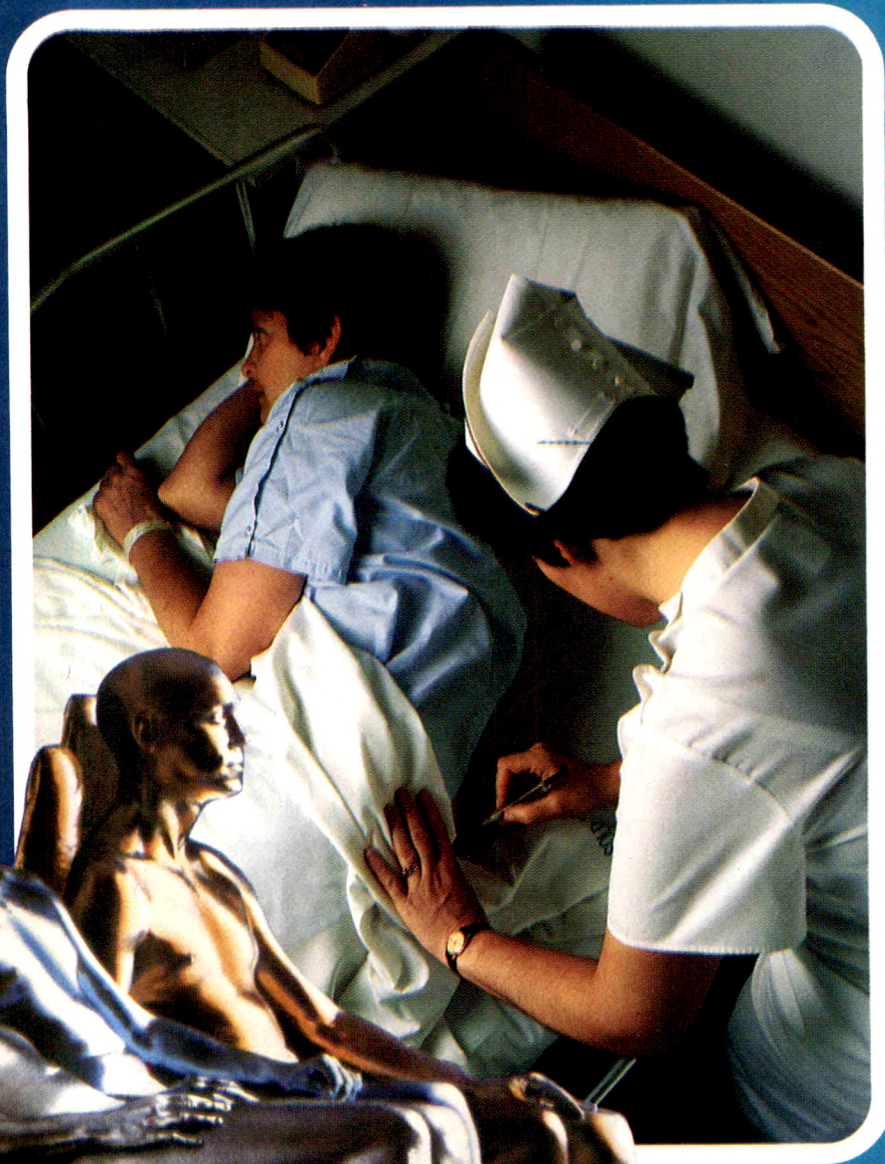


INJECTABLE
VERSED[®]
brand of
midazolam HCl
equivalent to 5 mg/mL
Roche 

Please note Dosage and Administration Guidelines and see references and summary of product information on last pages of this advertisement.

The advantage in premedication

Virtually painless faster sedative



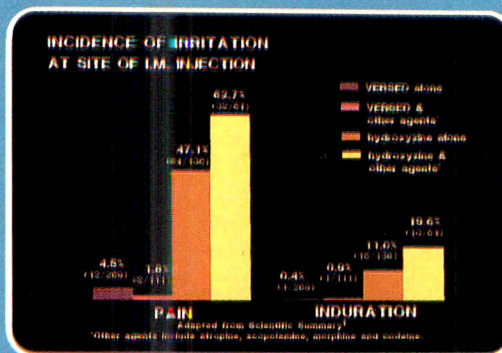
on injection... and amnestic action

Virtually painless

The first stable water-soluble benzodiazepine, VERSED administered intramuscularly produces less pain, induration or tissue irritation than hydroxyzine I.M.¹

Sedates faster

In double-blind premedication studies, onset of sedation was significantly faster and more pronounced with VERSED I.M. than with hydroxyzine I.M. After 15 minutes, 43% of 149 patients treated with VERSED had reached the most desirable levels of sedation compared to only 19% of 101 patients treated with hydroxyzine.²



Diminishes recall with a single I.M. injection

Patients treated with VERSED I.M. had significantly less recall of memory cards (7/26) shown during the preanesthetic period than patients treated with hydroxyzine (26/28).¹ Amnesia was greatest 30 to 60 minutes after administration. And when VERSED was given with scopolamine, the period of diminished recall extended to 90 minutes.¹

Compatible with other agents in the same syringe

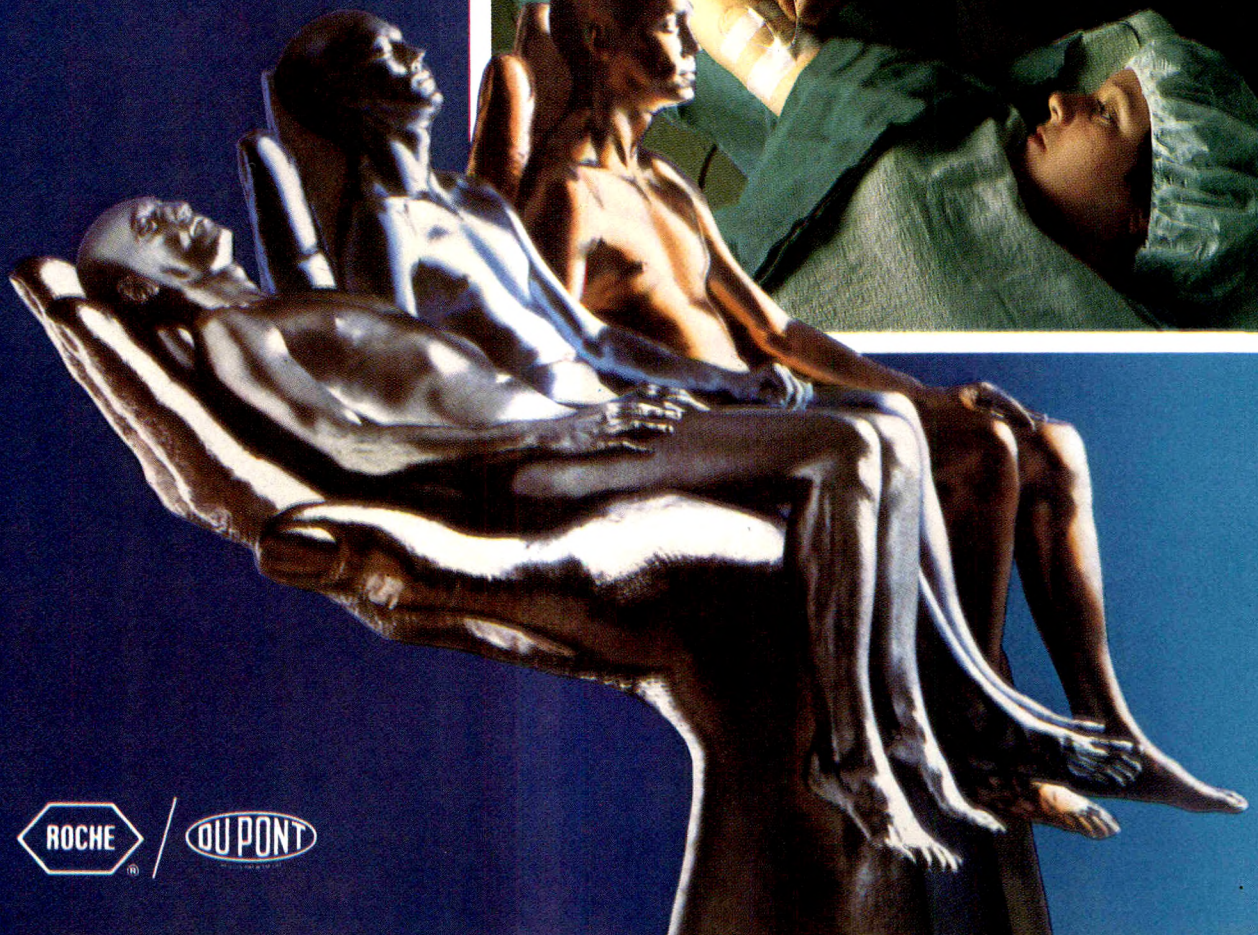
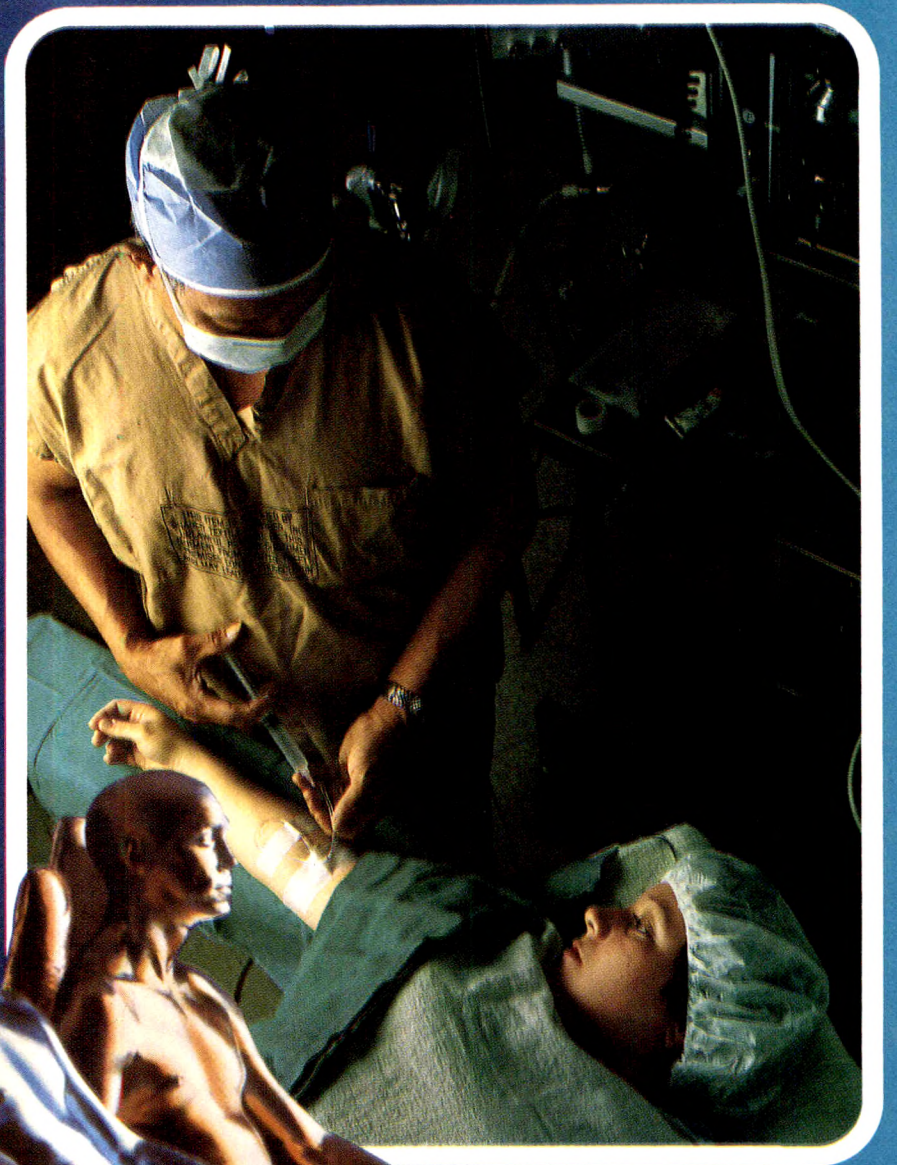
VERSED can be mixed in the same syringe with other frequently used premedicants: morphine sulfate, meperidine, atropine sulfate or scopolamine.

INJECTABLE
VERSED[®]
brand of
midazolam HCl Roche ^{IV}

Please note Dosage and Administration Guidelines and see references and summary of product information on last pages of this advertisement.

The advantage in I.V. conscious sedation

Superior amnestic effect

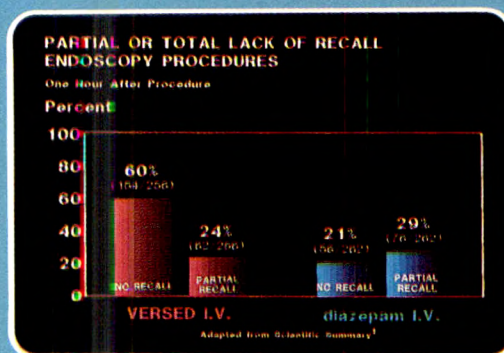


less tissue irritation

Significantly less recall

In double-blind, multicenter studies, patients treated with VERSED had significantly less recall of endoscopic procedures than patients receiving diazepam. Of 256 VERSED patients, well over half—60%—had no recall of their procedures when questioned one hour later. By contrast, only 21% of 262 diazepam patients had a similar lack of recall.¹

Use of a topical anesthetic for peroral procedures and narcotic premedication for bronchoscopies is recommended.



Less irritation

VERSED produced less pain or burning during I.V. administration than diazepam. VERSED also produced less postprocedural irritation: One week following I.V. administration, only 1.4% of 512 patients who received VERSED had tenderness of the vein compared with 3.0% of 503 patients who received diazepam ($P=0.07$).²

Faster onset

In the majority of clinical studies, the time required to reach the end point of slurred speech was significantly shorter when patients received VERSED I.V. rather than diazepam I.V. For most procedures, mean time to achieve sedation with VERSED ranged from 2.8 to 4.8 minutes, compared to a range of 2.6 to 9.0 minutes with diazepam.¹

As a standard precaution, prior to the I.V. administration of VERSED in any dose, oxygen and resuscitative equipment should be immediately available and a person skilled in maintaining a patent airway and supporting ventilation should be present. Extra care should be observed in the elderly or debilitated (such as lowering dosage by 25% to 30%), and in those with limited pulmonary reserve. Dosage of VERSED should also be lowered by about 25% to 30% if narcotic premedication is used. Caution patients against driving or operating hazardous machinery after receiving VERSED.

INJECTABLE
VERSED[®]
brand of
midazolam HCl / Roche 

Please note Dosage and Administration Guidelines and see references and summary of product information on last pages of this advertisement

The advantage in anesthetic induction and

Smooth induction...



balanced anesthesia

smooth emergence

Smooth induction of anesthesia

Intravenous VERSED provides induction of general anesthesia, prior to administration of other anesthetic agents, as effectively as thiopental in properly premedicated patients.¹ And it does so with significantly less apnea. Among 155 patients who received narcotic premedication and then VERSED, 37% had apnea, compared to 54% of 137 premedicated patients given thiopental.²

The initial dose of VERSED I.V. should be given over 20 to 30 seconds and titrated to desired effect. Avoid intra-arterial injection or extravasation. (See Warnings section of summary of product information.)

Dosages of VERSED should be lowered if sedative or narcotic premedication is used.

Minimal adverse hemodynamic effects

While the hemodynamic effects of VERSED I.V. do not differ significantly from those of thiopental, they are somewhat less pronounced.¹ Standard resuscitative equipment should be available, however, and extra care observed in elderly or debilitated patients (such as lowering dosage by 25% to 30%), and in patients with limited pulmonary reserve. VERSED should be administered as an induction agent only by a person trained in anesthesiology.

Valuable as a component of balanced anesthesia for short surgical procedures

VERSED not only works rapidly, it's easily titrated during balanced anesthesia.

Compatible—ready to use

VERSED is compatible with 5% dextrose in water, normal saline and lactated Ringer's solution. No reconstitution or refrigeration is needed. VERSED is available in unit-dose and multidose vials and Tel-E-Ject[®] disposable syringes.

INJECTABLE
VERSED[®]
brand of
midazolam HCl Roche 

Please note Dosage and Administration Guidelines and see references and summary of product information on last pages of this advertisement.

Administration

VERSED is contraindicated in patients with a known hypersensitivity to the drug. Benzodiazepines are contraindicated in patients with acute narrow angle glaucoma; however, they may be used in patients with open angle glaucoma only if they are receiving appropriate therapy.



ROCHE / DU PONT
NEW U.S. PAT. IN THE OFF.

INJECTABLE
VERSED
brand of
midazolam HCl Roche (C)

References: 1. VERSED® (brand of midazolam HCl/Roche) (U), Scientific Summary, Roche Laboratories, Nutley, NJ, 1986. 2. Data on file (Doc. #069-001-004, -007), Hoffmann-La Roche Inc., Nutley, NJ.

VERSED® (brand of midazolam HCl/Roche) INJECTION

Before prescribing, please consult complete product information, a summary of which follows:

INDICATIONS: IM: preoperative sedation; to impair memory of perioperative events. IV: conscious sedation prior to short diagnostic or endoscopic procedures, alone or with a narcotic; induction of general anesthesia before administration of other anesthetic agents; as a component of intravenous supplementation of nitrous oxide and oxygen (balanced anesthesia) for short surgical procedures (longer procedures have not been studied). When used IV, VERSED is associated with a high incidence of partial or complete impairment of recall for the next several hours.

CONTRAINDICATIONS: Patients with known hypersensitivity to the drug. Benzodiazepines are contraindicated in patients with acute narrow angle glaucoma; may be used in open angle glaucoma only if patients are receiving appropriate therapy.

WARNINGS: PRIOR TO IV ADMINISTRATION OF VERSED IN ANY DOSE, ENSURE THAT OXYGEN AND RESUSCITATIVE EQUIPMENT FOR MAINTAINING A PATENT AIRWAY AND SUPPORT OF VENTILATION ARE IMMEDIATELY AVAILABLE. IV VERSED depresses respiration, and opioid agonists and other sedatives can add to this depression; should be administered as induction agent only by a person trained in general anesthesia.

Do not administer in shock, coma, acute alcohol intoxication with depression of vital signs.

Guard against unintended intra-arterial injection; hazards in humans unknown. Avoid extravasation.

Higher risk surgical or debilitated patients require lower dosages for induction of anesthesia, premedicated or not.

Patients with chronic obstructive pulmonary disease are unusually sensitive to the respiratory depressant effect of VERSED. Patients with chronic renal failure have a 1.5- to 2-fold increase in elimination half-life, total body clearance and volume of distribution of midazolam. Patients with congestive heart failure have a 2- to 3-fold increase in the elimination half-life and volume of distribution of midazolam. Patients over 55 require lower dosages for induction of anesthesia, premedicated or not. Because elderly patients frequently have inefficient function of one or more organ systems, and because dosage requirements have been shown to decrease with age, reduce initial dosage and consider possibility of a profound and/or prolonged effect.

Concomitant use of barbiturates, alcohol or other CNS depressants may increase the risk of underventilation or apnea and may contribute to profound and/or prolonged drug effect. Narcotic premedication also depresses the ventilatory response to carbon dioxide stimulation.

Hypotension occurred more frequently in the conscious sedation studies in patients premedicated with narcotic.

Gross tests of recovery from the effects of VERSED cannot alone predict reaction time under stress. This drug is never used alone during anesthesia, and the contribution of other perioperative drugs and events can vary. The decision as to when patients may engage in activities requiring mental alertness must be individualized; it is recommended that no patient should operate hazardous machinery or a motor vehicle until the effects of the drug, such as drowsiness, have subsided or until the day after anesthesia, whichever is longer.

Usage in Pregnancy: An increased risk of congenital malformations associated with the use of benzodiazepines (diazepam and chlordiazepoxide) has been suggested in several studies. If VERSED is used during pregnancy, apprise the patient of the potential hazard to the fetus.

PRECAUTIONS: General: Increased cough reflex and laryngospasm may occur with peroral endoscopic procedures. Use topical anesthetic and make necessary countermeasures available; use narcotic premedication for bronchoscopy. Decrease intravenous doses by 25% to 30% for elderly and debilitated patients. These patients will also probably take longer to recover completely after VERSED for induction of anesthesia. VERSED does not protect against increased intracranial pressure or circulatory effects noted following administration of succinylcholine.

VERSED does not protect against increased intracranial pressure or against the heart rate rise and/or blood pressure rise associated with endotracheal intubation under light general anesthesia.

Information for patients: Communicate the following information and instructions to the patient when appropriate:

1. Inform your physician about any alcohol consumption and medicine you are now taking, including nonprescription drugs. Alcohol has an increased effect when consumed with benzodiazepines; therefore, caution should be exercised regarding simultaneous ingestion of alcohol and benzodiazepines. 2. Inform your physician if you are pregnant or are planning to become pregnant. 3. Inform your physician if you are nursing.

Drug interactions: The hypnotic effect of intravenous VERSED is accentuated by premedication, particularly narcotics (e.g., morphine, meperidine, fentanyl) and also secobarbital and Innovar (fentanyl and droperidol). Consequently, adjust the dosage of VERSED according to the type and amount of premedication.

A moderate reduction in induction dosage requirements of thiopental (about 15%) has been noted following use of intramuscular VERSED for premedication.

The use of VERSED as an induction agent may result in a reduction of the inhalation anesthetic requirement during maintenance of anesthesia.

VERSED® (brand of midazolam HCl/Roche) INJECTION

Although the possibility of minor interactive effects has not been fully studied, VERSED and pancuronium have been used together in patients without noting clinically significant changes in dosage, onset or duration. VERSED does not protect against the characteristic circulatory changes noted after administration of succinylcholine or pancuronium, or against the increased intracranial pressure noted following administration of succinylcholine. VERSED does not cause a clinically significant change in dosage, onset or duration of a single intubating dose of succinylcholine.

No significant adverse interactions with commonly used premedications or drugs used during anesthesia and surgery (including atropine, scopolamine, glycopyrrolate, diazepam, hyaloxazine, d-tubocurarine, succinylcholine and nondepolarizing muscle relaxants) or topical local anesthetics (including lidocaine, dyclonine HCl and Cetacaine) have been observed.

Drug/abuse test interactions: Midazolam has not been shown to interfere with clinical laboratory test results.

Carcinogenesis, mutagenesis, impairment of fertility: Midazolam maleate was administered to mice and rats for two years. At the highest dose (80 mg/kg/day) female mice had a marked increase in incidence of hepatic tumors and male rats had a small but significant increase in benign thyroid follicular cell tumors. These tumors were found after chronic use, whereas human use will ordinarily be of single or several doses.

Midazolam did not have mutagenic activity in tests that were conducted.

A reproduction study in rats did not show any impairment of fertility at up to ten times the human IV dose.

Pregnancy: Teratogenic effects: Pregnancy Category D. See WARNINGS section. Midazolam maleate injectable, at 5 and 10 times the human dose, did not show evidence of teratogenicity in rabbits and rats.

Labor and delivery: The use of injectable VERSED in obstetrics has not been evaluated. Because midazolam is transferred transplacentally and because other benzodiazepines given in the last weeks of pregnancy have resulted in neonatal CNS depression, VERSED is not recommended for obstetrical use.

Nursing mothers: It is not known whether midazolam is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when injectable VERSED is administered to a nursing woman.

Pediatric use: Safety and effectiveness of VERSED in children below the age of 18 have not been established.

ADVERSE REACTIONS: Fluctuations in vital signs following parenteral administration were the most frequently seen findings and included decreased tidal volume and/or respiratory rate decrease (23.3% of patients following IV and 10.8% of patients following IM administration) and apnea (15.4% of patients following IV administration), as well as variations in blood pressure and pulse rate. These are common occurrences during anesthesia and surgery and are affected by the lightening or deepening of anesthesia, instrumentation, intubation and use of concomitant drugs.

In the conscious sedation studies, hypotension occurred more frequently after IV administration in patients concurrently premedicated with meperidine. During clinical investigations, three cases (0.2%) of transient fall in blood pressure greater than 50% were reported during the induction phase.

Following IM injection: headache (1.3%); local effects at IM site: pain (3.7%), induration (0.5%), redness (0.5%), muscle stiffness (0.3%). Following IV administration: hiccoughs (3.9%), nausea (2.8%), vomiting (2.6%), coughing (1.3%), "oversedation" (1.6%), headache (1.5%), drowsiness (1.2%); local effects at the IV site: tenderness (5.6%), pain during injection (5.0%), redness (2.6%), induration (1.7%), phlebitis (0.4%). Other effects (<1%) mainly following IV administration: **Respiratory:** Laryngospasm, bronchospasm, dyspnea, hyperventilation, wheezing, shallow respirations, airway obstruction, tachypnea. **Cardiovascular:** Bigeminy, premature ventricular contractions, vasovagal episode, tachycardia, nodal rhythm. **Gastrointestinal:** Acid taste, excessive salivation, retching. **CNS/Neuromuscular:** Retrograde amnesia, euphoria, confusion, argumentativeness, nervousness, agitation, anxiety, grogginess, restlessness, emergence delirium or agitation, prolonged emergence from anesthesia, dreaming during emergence, sleep disturbance, insomnia, nightmares, tonic/clonic movements, muscle tremor, involuntary movements, athetoid movements, ataxia, dizziness, dysphoria, slurred speech, dysphonia, paresthesia. **Special sense:** Blurred vision, diplopia, nystagmus, pinpoint pupils, cyclic movements of eyelids, visual disturbance, difficulty focusing eyes, ears blocked, loss of balance, lightheadedness. **Integumentary:** Hives, hive-like elevation at injection site, swelling or feeling of burning, warmth or coldness at injection site, rash, pruritus. **Miscellaneous:** Yawning, lethargy, chills, weakness, toothache, faint feeling, hematoma.

Drug Abuse and Dependence: Available data concerning the drug abuse and dependence potential of midazolam suggest that its abuse potential is at least equivalent to that of diazepam.

DOSEAGE AND ADMINISTRATION: Individualize dosage. Elderly and debilitated patients generally require lower doses. Adjust dose of IV VERSED according to type and amount of premedication. **IM use:** Inject deep in large muscle mass. **IV use:** Administer slowly: rapid injection may cause respiratory depression or apnea requiring assisted or controlled ventilation. Administer initial dose over 20 to 30 seconds for induction of general anesthesia. May be mixed in the same syringe with morphine sulfate, meperidine, atropine sulfate or scopolamine. Compatible with 5% dextrose in water, 0.9% sodium chloride and lactated Ringer's solution.

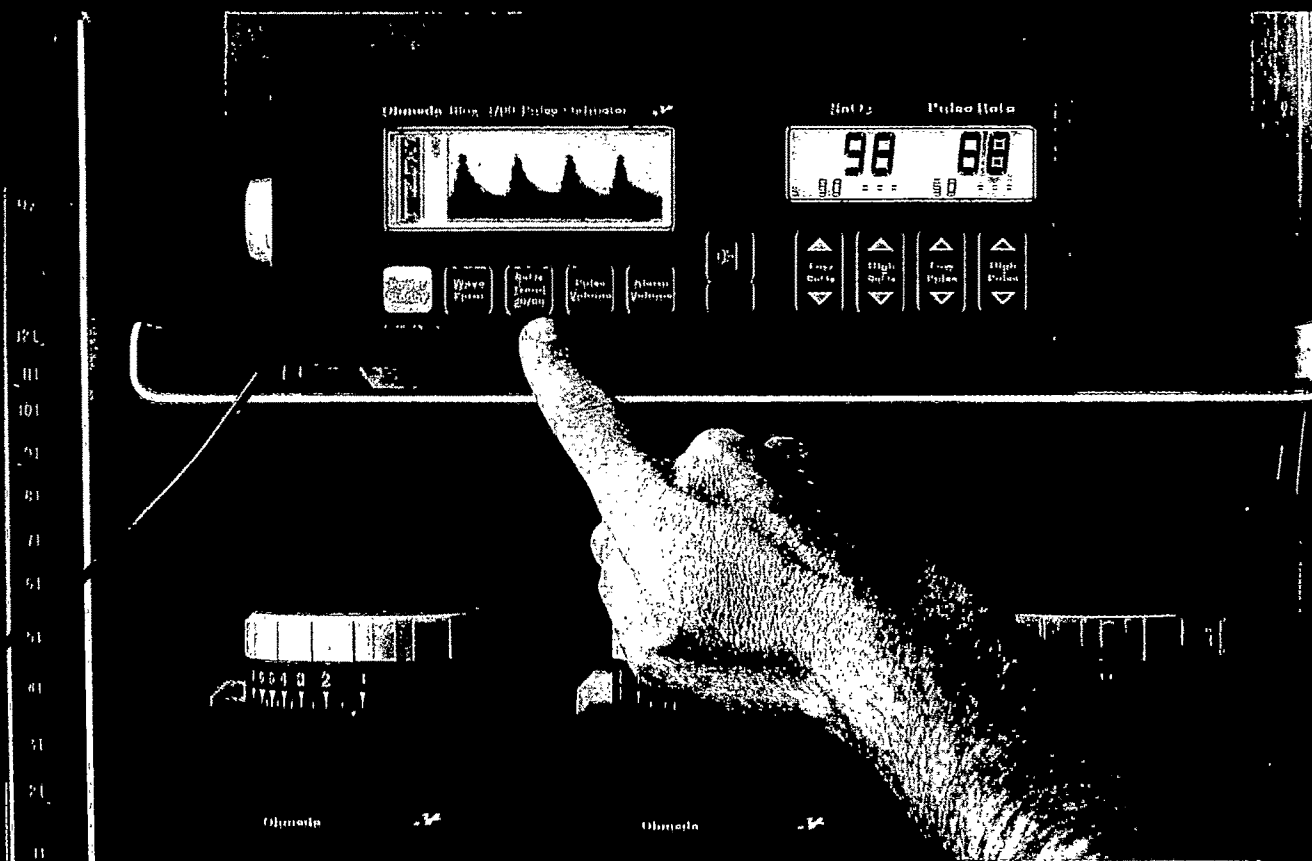
OVERDOSEAGE: Overdosage has not been reported, but manifestations would resemble those observed with other benzodiazepines (e.g., sedation, somnolence, confusion, impaired coordination, diminished reflexes, coma, untoward effects on vital signs). No specific organ toxicity would be expected.

SUPPLIER: All packages contain midazolam hydrochloride equivalent to 5 mg/mL. Vials: 1 mL (5 mg), 2 mL (10 mg), 5 mL (25 mg), 10 mL (50 mg)—boxes of 10; Tel-E-Ject® disposable syringes; 2 mL (10 mg)—boxes of 10.



ROCHE LABORATORIES
Division of Hoffmann-La Roche Inc.
Nutley, New Jersey 07110

Ohmeda



Judgment. It takes everything you've got.

That's why we built the new **Ohmeda Biox 3700 Pulse Oximeter**. Because good patient management depends on your judgment—and on a consistent source of thorough, accurate information.

More data for better decisions.

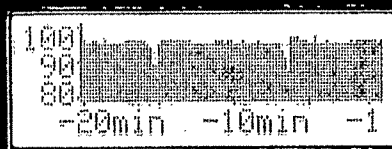
Only the Ohmeda Biox 3700 gives you a **Plethysmographic Wave-form Display** for a continuous representation of blood volume changes. Plus a **Signal Strength Indicator** that keeps you updated on the pulsatile signal quality. Add our digital SaO_2 and pulse rate readings, and you have an unprecedented view of the real-time conditions at the probe site.

And that's just the beginning. The 3700's clear, highly visible user messages keep you informed about potential monitoring interruptions. And in alarm situations, the 3700

will alert you to the condition which needs immediate attention.

Enjoy the information advantage.

For the first time, your patient's immediate SaO_2 history is at your fingertips. Because a single touch activates our 20 and 60 Minute



20 minute Trend Display for immediate SaO_2 history.

Trend Display. You can even access up to 8 hours of stored SaO_2 and pulse rate information for subsequent hard-copy recording or computer printout. There's never been a more accessible, versatile oximetry tool for patient management and assessment.

The definitive oximeter? You be the judge.

Ohmeda has been setting the standards in anesthesia technology for 75 years. And Ohmeda Biox designed the first practical pulse oximeters. So we know exactly what you need from an oximeter. And the 3700 has it all.

So call today for a demonstration of the remarkable Ohmeda Biox 3700. Because only you can make those crucial judgments. And only data of this quality is good enough to support them.

For more information write or contact an Ohmeda representative at:
Ohmeda
4765 Walnut Street, Boulder, CO 80301
1 800 652 2469 1 800 345 2700
303 447 9842 Telex 296 445

Ohmeda oximetry. Right from the start.

The Effect of β -Adrenergic Blockade on the Cardiovascular Response to Diltiazem or Verapamil in Dogs

Kathleen B. Sullivan, MD, and Patricia A. Kapur, MD

SULLIVAN KB, KAPUR PA. The effect of β -adrenergic blockade on the cardiovascular response to diltiazem or verapamil in dogs. 1986;65:1099-1106.

Diltiazem or verapamil were each given at two different infusion rates to pentobarbital-anesthetized dogs with or without a concurrent infusion of propranolol. Changes in cardiovascular function, in reflex activation as reflected by circulating catecholamine levels, and in the chronotropic response to an exogenous β -adrenergic agonist, isoproterenol, were measured. When administered alone, diltiazem or verapamil, at plasma concentrations of 160 and 370 ng/ml, or 230 and 500 ng/ml, respectively, prolonged atrioventricular conduction and caused systemic vasodilation with a decrease in mean arterial pressure. Cardiac index increased, associated with an increase in arterial norepinephrine level. Heart rate increased with the lower level of verapamil; left ventricular dP/dt increased with both levels of verapamil and at the higher level of diltiazem. Plasma propranolol levels of approximately 35 ng/ml were well tolerated in the absence of diltiazem or verapamil. When added to diltiazem or verapamil, propranolol resulted in an increase

in systemic vascular resistance to near control values; a decrease in cardiac index, left ventricular dP/dt, and heart rate; and worsened atrioventricular conduction. Three of nine animals in the high verapamil-propranolol group were unable to maintain a mean arterial pressure greater than 50 mm Hg, and developed a low cardiac index with an elevated systemic vascular resistance, despite very high levels of circulating catecholamines. Compared to the anesthetized state, greater amounts of isoproterenol were needed to effect the same increase in heart rate with the addition of diltiazem, verapamil, or propranolol alone. The combined competitive and noncompetitive β -adrenergic blockade associated with diltiazem or verapamil plus propranolol demonstrated that the ability to respond to an exogenously administered β -adrenergic agonist may be seriously impaired with these drug combinations.

Key Words: HEART—myocardial function. PHARMACOLOGY—diltiazem, verapamil, propranolol. SYMPATHETIC NERVOUS SYSTEM, β -ADRENERGIC BLOCKADE—propranolol, catecholamines.

Verapamil and diltiazem are calcium channel blocking drugs currently in widespread use for a variety of cardiovascular disorders. Although of different chemical structures, each exerts some of its pharmacologic effects by inhibition of inward calcium flux through slow ionic channels of excitable cell membranes, especially in vascular smooth muscle and in the myocardium (1). β -Adrenergic blocking agents also may decrease intracellular calcium availability in the myocardium by decreasing the number of slow channels available for calcium flux (2). Chronic combined calcium channel and β -adrenergic blockade has proven useful in the treatment of ischemic heart disease (3-5),

but occasional adverse effects have been reported from their coadministration. Particular caution is needed when considering these drugs for patients with preexisting sinus or atrioventricular nodal disease and/or compromised left ventricular function. After combined intravenous administration of verapamil and various β -adrenergic blockers for the treatment of supraventricular tachyarrhythmias, severe combined depressant effects including hypotension, sinus arrest, cardiogenic shock, and death have been reported (6,7). The possibility of depression from combined diltiazem and β -blockade has not been well substantiated (5,8).

This study was designed to investigate the effects of adding propranolol to two plasma levels of verapamil or diltiazem. Changes in hemodynamic values, in reflex activation as reflected by circulating catecholamine levels, and in myocardial sensitivity to β -adrenergic stimulation as assessed by the heart rate response to an exogenous β -agonist, isoproterenol, were measured.

Presented in part at the annual meeting of the American Society of Anesthesiologists, San Francisco, California, October 14, 1985.

Received from the Department of Anesthesiology, UCLA School of Medicine, Los Angeles, California. Accepted for publication June 6, 1986.

Address correspondence to Dr. Kapur, Department of Anesthesiology, UCLA School of Medicine, Los Angeles, CA 90024.

PROTOCOL

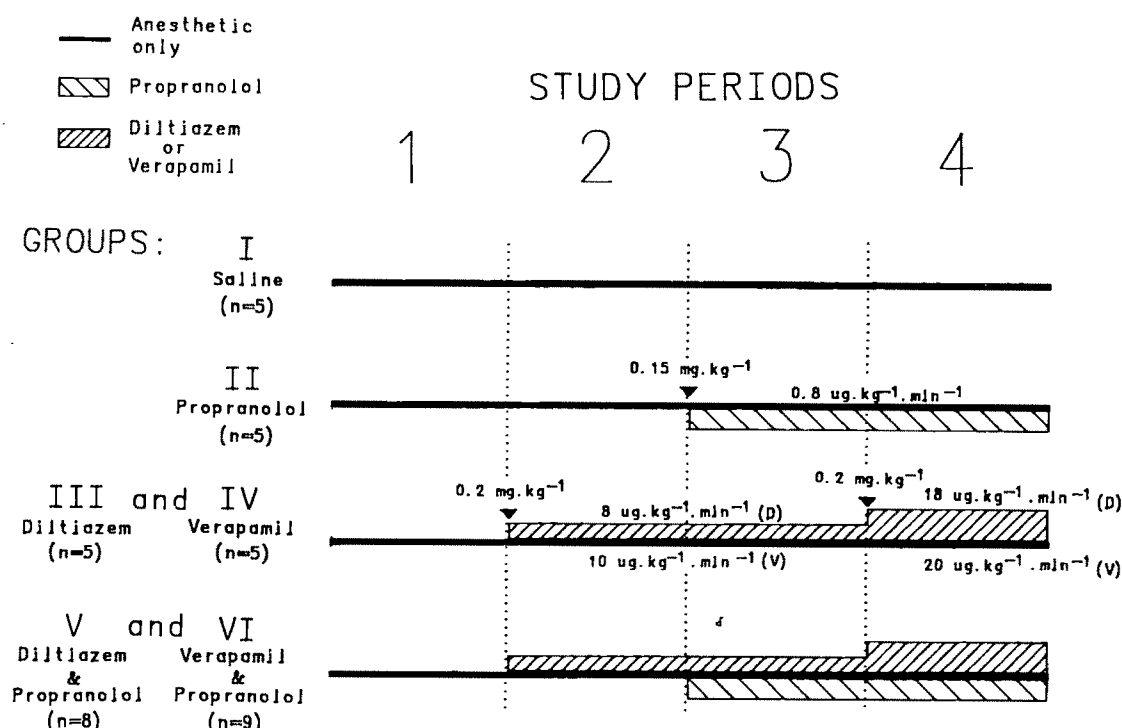


Figure 1. Experimental protocol. During period 1, all dogs received pentobarbital alone, had control measurements and plasma samples taken, underwent an isoproterenol dose-response test to assess the maximum changes in heart rate to various doses of isoproterenol, and had repeat measurements and plasma samples taken 20 min after the last isoproterenol dose. In periods 2, 3, and 4, only saline, or else propranolol, diltiazem, verapamil, or the combination of propranolol with either of the calcium channel blockers, were given to the various groups as detailed in the figure (bolus doses and continuous infusion rates as indicated). Groups V and VI received the same boluses and infusion rates for propranolol and diltiazem or propranolol and verapamil as shown for groups II, III, and IV. Study periods 2, 3, and 4 consisted of the following events: initiation of the appropriate bolus and infusion; measurements and plasma samples at 2, 30, and 35 min; the isoproterenol dose-response test; and the postisoproterenol repeat measurements. D, diltiazem infusion rates; V, verapamil infusion rates.

Methods

Thirty-seven experiments were performed on 16 healthy mongrel dogs of either sex weighing 21 ± 1 kg (mean \pm SE), cared for in accordance with the American Association for Accreditation of Laboratory Animal Care. A cannula was inserted into a peripheral vein for fluid and drug administration. The nonpremedicated dogs were anesthetized with a slow intravenous injection of pentobarbital, 30 mg/kg, followed by a continuous infusion of pentobarbital, 5 mg.kg⁻¹.hr⁻¹. After tracheal intubation, ventilation

was controlled with a Harvard Apparatus Dual Phase Control Respirator Pump, model 623, using 40% oxygen in air to maintain P_{aCO_2} between 30–37 mm Hg as determined by serial arterial blood gas measurements (Instrumentation Laboratories Analyzer, Model 813). Sodium chloride, 0.9%, was infused at a rate of 5–7 ml.kg⁻¹.hr⁻¹. To maintain pH between 7.35 and 7.45, NaHCO₃ was administered intravenously as needed. Temperature was maintained between 37° and 39°C with a circulating water blanket and a heating lamp. Instrumentation included a 4-lead ECG, a percutaneous femoral arterial catheter, a percutaneous, flow-directed, thermistor-tipped, pulmonary artery catheter, and a micromanometer-tipped catheter (Millar Instruments Inc.) introduced into the left ventricle (LV) from a femoral artery. Lead II of the ECG, heart rate (HR), phasic and mean arterial pressure (MAP), pulmonary arterial pressure, central venous pressure (CVP), and LV pressure, as well as the electronically derived LV dP/dt, were all continuously recorded, along with intermittent recordings of pulmonary capillary wedge pressure (PCW) on a Hewlett-Packard polygraph, model 7758A. The ECG was intermittently recorded at fast paper speed (100 mm/sec) for measurement of PR intervals. Cardiac outputs were measured in triplicate by thermodilution (Edwards Laboratories, Cardiac Output Computer, model

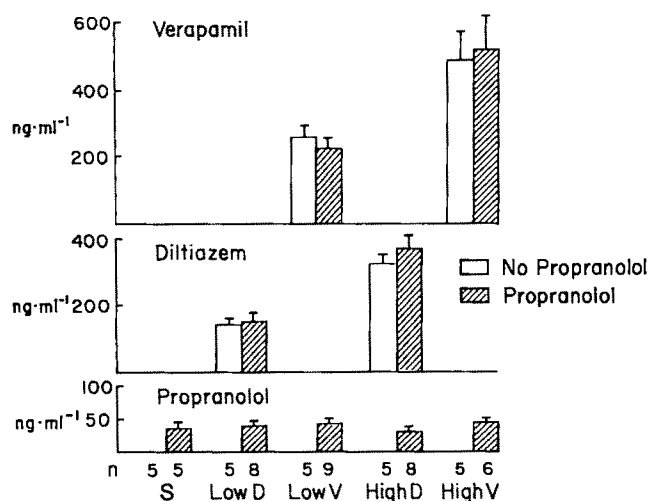


Figure 2. Plasma verapamil, diltiazem, or propranolol levels (mean \pm SE) at 35 min of period 3 or 4. S, groups I and II at period 3; Low D, groups III and V at period 3; High D, groups III and V at period 4; Low V, groups IV and VI at period 3; High V, groups IV and VI at period 4 (see Fig. 1). There were no differences between the pairs of verapamil or diltiazem levels, with or without propranolol, or among the five propranolol levels shown.

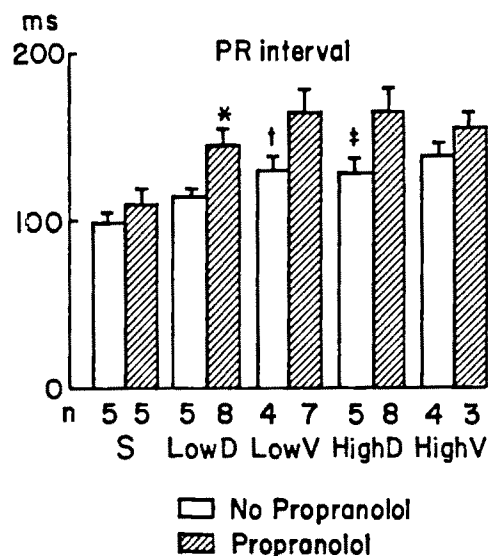


Figure 3. PR interval of the electrocardiogram (mean \pm SE) for the same groups as Figure 2. $\dagger P < 0.05$ compared to no calcium channel blocker; $\ddagger P < 0.05$ compared to low calcium channel blocker; $*$ $P < 0.05$ compared to equivalent group without propranolol.

9520). Cardiac index (CI) and systemic and pulmonary vascular resistance (SVR, PVR) were calculated. Propranolol, verapamil, diltiazem, norepinephrine (NE), and epinephrine (EPI) plasma levels were assayed using high performance liquid chromatography (9-11). The lower limits of the assay for the drugs was approximately 1 ng/ml and for EPI and NE 20 pg/ml. Hematocrit and serum levels of electrolytes (Na^+ , Cl^- , K^+), glucose, and calcium were determined at regular intervals throughout each study.

To assess β -adrenergic responsiveness, the maximal change in heart rate to each of at least three graded doses of isoproterenol was measured four times in each experiment. Doses of isoproterenol used were 0.02, 0.05, 0.15, 0.50, 1.00, and 2.00 $\mu\text{g}/\text{kg}$. As testing proceeded, an isoproterenol dose-response curve was constructed plotting change in heart rate as a function of the logarithm of the isoproterenol dose. Doses were chosen to include the straight central portion of the sigmoidal dose-response curve thereby obtained. To make comparisons among dogs receiving different isoproterenol dose combinations, a double reciprocal plot of $1/(\text{change in heart rate})$ vs $1/(\text{isoproterenol dose})$ was constructed for each animal for each isoproterenol test. A "best fit" line was then generated by a linear regression technique. These derived lines were very close in value and conformed to the raw data curves for each dog when transformed back to a semilog form. Values for changes in heart rate for intermediate isoproterenol doses were then deter-

mined from the equations of these lines and the mean changes in heart rate were plotted against the logarithm of the respective isoproterenol dose for each of the treatment groups.

The study design is shown in Figure 1. In all experiments, a 30-min stabilization period followed instrumentation and ventilator and pH adjustments. Each experiment was subdivided into four measurement periods. During period 1, all dogs received anesthetic alone. Control hemodynamic variables, ECG, and arterial samples for measurements of catecholamines, drug levels, electrolytes, hematocrit, and blood gas tensions were obtained. A control isoproterenol dose-response curve was then constructed allowing 1C min between each isoproterenol dose with 20 min after the last dose for dissipation of isoproterenol effects. A second set of measurements were then taken for comparison with preisoproterenol values and to serve as the control for the succeeding measurement period. The experiments were then divided into 6 groups for the remainder of the protocol: I, control ($n = 5$); II, propranolol ($n = 5$); III, diltiazem ($n = 5$); IV, verapamil ($n = 5$); V, diltiazem and propranolol ($n = 8$); VI, verapamil and propranolol ($n = 9$). The structure of the last three measurement periods was as follows: control values were obtained; the appropriate drug or saline injections and infusions were started; complete hemodynamic measurements were made and arterial blood samples taken at 2, 30, and 3E min; as the drug infusion(s) continued, an isopro-

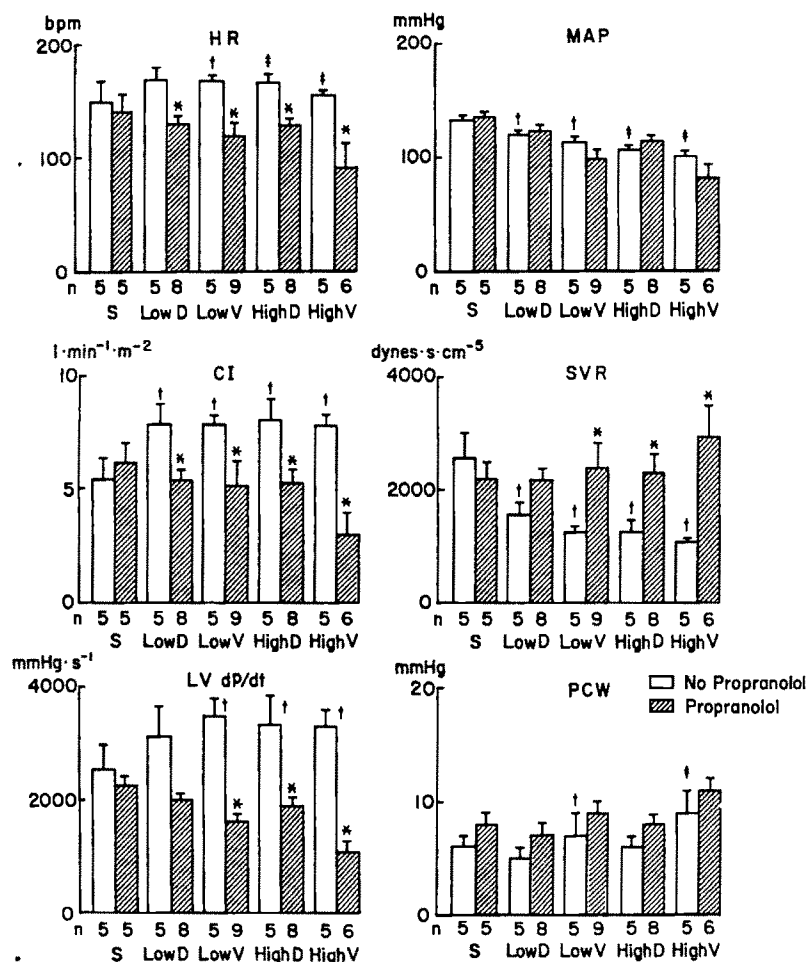


Figure 4. Hemodynamic values (mean \pm SE) for the same groups as Figure 2. † $P < 0.05$ compared to no calcium channel blocker; ‡ $P < 0.05$ compared to low calcium channel blocker, * $P < 0.05$ compared to equivalent group without propranolol.

terenol dose-response curve was constructed; and finally, the additional set of measurements were taken 20 min after the last isoproterenol dose. For conservation of animal resources, individual animals were recovered after each experiment and used for a total of up to three experiments each (different drug groups) with intervening intervals of at least two weeks between experiments.

The control group received only anesthetic throughout. In period 2, dogs in group II received only anesthetic, whereas diltiazem or verapamil was started in the four calcium channel blocker groups (III-VI). The doses of diltiazem and verapamil were 200 $\mu\text{g}/\text{kg}$ over 2 min followed by infusions of 8 or 10 $\mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$, respectively. In period 3, propranolol was added in three groups (II, V, and VI) to a background of saline, diltiazem, or verapamil, respectively. The propranolol dose was 150 $\mu\text{g}/\text{kg}$ over 2 min followed by an infusion of 0.8 $\mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$. In the fourth period, doses of calcium blockers were increased in groups III-VI. The bolus dose of 200 $\mu\text{g}/\text{kg}$ of diltiazem or verapamil was repeated and the in-

fusion rate increased to 18 or 20 $\mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$, respectively. An experiment was terminated if the MAP decreased below 50 mm Hg.

Statistical tests included analysis of variance and analysis of variance for repeated measures with Bonferroni modified t -tests, as well as nonpaired t -tests. A P value of less than 0.05 was considered statistically significant.

Results

Temperature, hematocrit, electrolyte levels, and arterial blood gas tensions remained within normal limits throughout each study in all groups of dogs. No significant changes in any of the variables were measured for the entire duration of the experimental protocol in the control group (receiving pentobarbital alone) or within periods 1 and 2 in group II, which received only anesthetic during those times. There were also no significant differences among any of the six groups during period 1 when all dogs were receiving only anesthetic. Within the first three measurement pe-

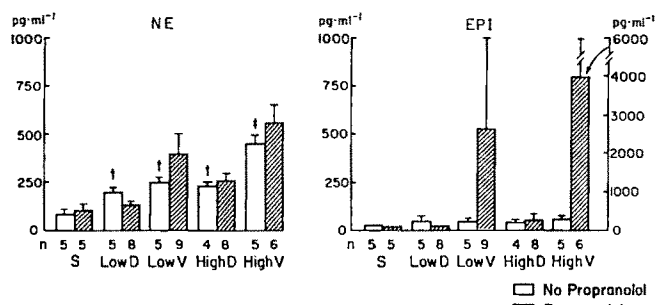


Figure 5. Arterial plasma levels of norepinephrine (NE) and epinephrine (EPI) for the same groups as Figure 2. $\dagger P < 0.05$ compared to no calcium channel blocker; $\ddagger P < 0.05$ compared to low calcium channel blocker.

riods, there were no differences in hemodynamic variables, drug levels, or catecholamine levels between the control and postisoproterenol values in the first period, or among the 30 min, 35 min, and postisoproterenol measurements in the second and third periods, indicating fairly steady conditions and lack of lasting perturbation by the isoproterenol test. In period 4, the 30 and 35 min values differed from the post-isoproterenol values in only two instances: 1) atrioventricular conduction block developed after isoproterenol in three diltiazem plus propranolol dogs (group V), and 2) NE levels increased above the 35 min values with verapamil alone (group IV) after the isoproterenol test. Otherwise, in period 4, as well, all other variables were equivalent between the 30 min, 35 min, and postisoproterenol measurements.

Comparisons within groups, as well as time-matched comparisons between groups were performed to assess the effects of adding calcium channel blockers or propranolol. Because the 30 min, 35 min, and postisoproterenol values were equivalent in most circumstances, the 35 min values were used for comparison between the various drug states, and are used for the figures.

Plasma drug levels for diltiazem, verapamil, and propranolol are shown in Figure 2. Mean diltiazem levels were approximately 160 ng/ml in period 3 and 370 ng/ml in period 4, whereas verapamil levels were approximately 230 ng/ml and 500 ng/ml respectively. Plasma levels of diltiazem or verapamil were significantly higher in time period 4 compared to period 3 as intended by the protocol. The diltiazem and verapamil levels were the same in groups III and V, and IV and VI, with or without propranolol, at low (period 3) and high (period 4) infusion rates (Fig. 1). The mean propranolol levels were between 32 and 42 ng/ml. There were no significant differences in propranolol levels among groups II, V, and VI during periods 3 and 4.

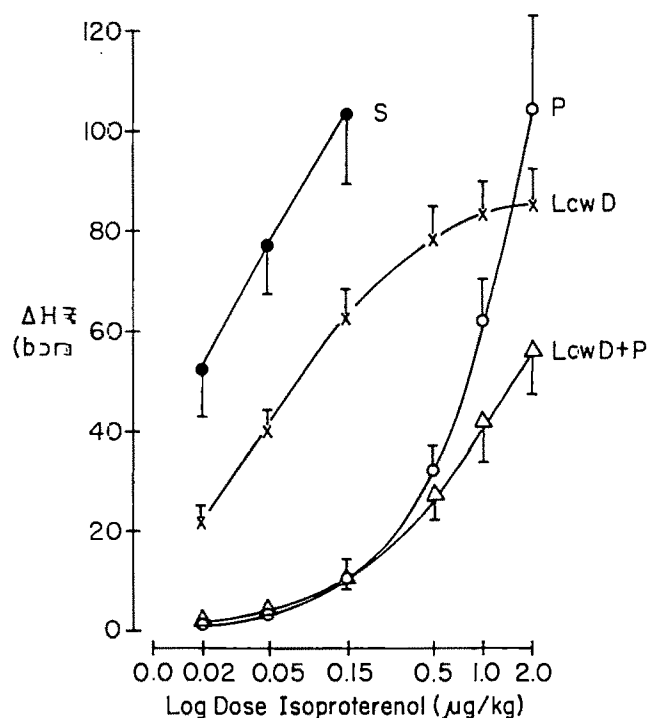


Figure 3. Semilogarithmic plot of the isoproterenol dose vs the mean of the maximal change in heart rate during study period 3: for the anesthetic alone (group I, S); propranolol only (group II, P); low levels of diltiazem alone (group III, Low D); and for the combination of low diltiazem with propranolol (group V, Low D + P).

Changes in PR intervals are shown in Figure 3. Low- and high-dose verapamil and high-dose diltiazem prolonged the PR interval. Propranolol did not affect PR interval when given alone, but worsened AV conduction when added to either calcium blocker in both dose ranges. Second or third degree conduction block was present in one of five dogs receiving low and high verapamil alone (group IV, periods 3 and 4), and two of nine and six of nine verapamil plus propranolol dogs at low and high verapamil levels respectively (group VI, periods 3 and 4). None of the diltiazem only dogs (group III, periods 3 and 4) developed high degree conduction block. Even with high diltiazem plus propranolol (group V, period 4), conduction block was only observed after isoproterenol testing, and only in three of eight dogs.

Hemodynamic changes are shown in Figure 4. Systemic vascular resistance decreased with low doses of diltiazem or verapamil. This effect persisted at higher plasma levels of both calcium channel blockers, without further decrease. Propranolol alone did not significantly affect SVR, but increased SVR when added to all calcium blocker groups except low diltiazem. The effect of adding propranolol to diltiazem or verapamil was to increase SVR back to values compa-

rable to those observed in the anesthetic alone group (group I) at the equivalent time period. Mean arterial pressure decreased with both diltiazem and verapamil alone in a dose-dependent manner. Adding propranolol had no effect on MAP in any group of the animals completing the study. However, three of nine dogs in the high verapamil plus propranolol group could not be included in the mean values depicted in the figures as they were removed from the study before the 35-min measurement because of an MAP of less than 50 mm Hg.

Heart rate increased significantly with low verapamil alone and then decreased when doses of either diltiazem or verapamil were increased. Cardiac index increased with both low diltiazem and low verapamil but did not further increase with the higher dose of either agent. Left ventricular dP/dt increased significantly with low verapamil and the higher dose of diltiazem. Increasing verapamil did not further increase LV dP/dt. Propranolol alone caused a small but significant decrease in HR during period 3 and in MAP during period 4. However, when propranolol was added to the calcium channel blockers at low or high levels, decreases occurred in HR, CI, and LV dP/dt. Pulmonary capillary wedge pressure was elevated with verapamil alone and tended to increase as the verapamil dose was increased. Adding propranolol to either calcium channel blockers did not significantly change PCW from that with the calcium blockers alone.

Plasma levels of NE and EPI are shown in Figure 5. Plasma NE levels increased with low doses of either diltiazem or verapamil and increased further in the high verapamil groups. Plasma NE levels did not change with the addition of propranolol to low diltiazem or verapamil, nor was there a significant difference in NE levels between either the high diltiazem or verapamil groups with or without propranolol. Very high EPI levels were observed in some dogs that received verapamil plus propranolol.

As stated earlier, three of the nine verapamil plus propranolol dogs were unable to complete the study and were not included in the statistical analysis. Shortly after the second verapamil bolus and the increase in the verapamil infusion, these dogs developed second degree or higher heart block with decreased HR, hypotension, low CI, low LV dP/dt, and elevated SVR coincident with very high catecholamine levels. High plasma EPI levels appeared to signal impending or manifest hemodynamic compromise.

Isoproterenol dose-response curves from time period 3 are shown in Figures 6 and 7. Propranolol alone shifted the curve to the right approximately 1.5 orders of magnitude. Diltiazem or verapamil alone flattened

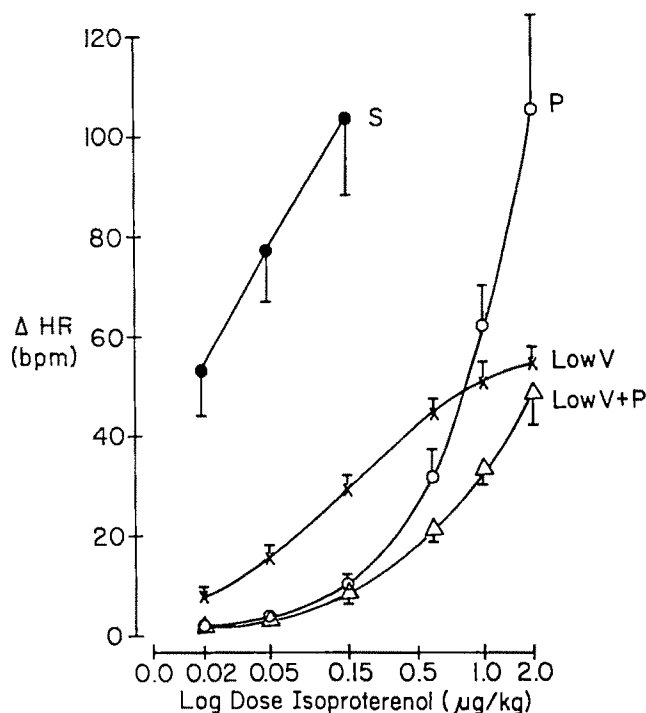


Figure 7. Semilogarithmic plot of the isoproterenol dose vs the means of the maximal change in heart rate during study period 3: for the anesthetic alone (group I, S); propranolol only (group II, P); low levels of verapamil alone (group IV, Low V); and for the combination of low verapamil with propranolol (group VI, Low V + P).

the dose-response curve and apparently lowered the maximum change in HR. The addition of propranolol to either diltiazem or verapamil shifted the flattened curve so that higher isoproterenol doses were required to cause the same change in HR.

Discussion

This model, designed to study the interaction between calcium channel blockers and β -adrenergic blocking agents, was hemodynamically and adrenergically stable throughout the course of the experiment (group I, pentobarbital alone). Intermittent isoproterenol testing caused only a transient perturbation of this stability.

The propranolol levels achieved in this study are considered in the low therapeutic range in man (12). Isoproterenol testing in this study demonstrated that β -adrenergic blockade was present to a degree sufficient to cause a 1.5 order of magnitude increase in the amount of isoproterenol required to cause a similar increase in heart rate. This degree of shift has been correlated with antianginal efficacy in man. Significant membrane stabilizing or local anesthetic ef-

fects associated with propranolol are probably of no significance with this dose range or plasma level (13), and the effect of combining propranolol and calcium channel blockers is presumably a result of the β -adrenergic blocking properties of propranolol.

When administered alone, the hemodynamic and adrenergic effects of diltiazem and verapamil were similar to each other. Direct vasodilation elicited a compensatory reflex response reflected in cardiovascular and humoral signs of increased adrenergic activity. This increased adrenergic activity, as reflected by elevations in plasma NE, was essentially unchanged when propranolol was added. However, with the β -adrenoceptor limb of the reflex response blocked, myocardial performance diminished, while presumably unopposed α -adrenergic activity resulted in elevation of SVR and, for the most part, maintenance of MAP. The combination of propranolol with verapamil leads to severe hemodynamic compromise in some animals at plasma levels of verapamil that were otherwise tolerated in non- β -blocked animals. In these instances, the addition of propranolol did cause a dramatic rise in catecholamines coincident with the onset of hemodynamic collapse. This did not occur in the diltiazem groups at the plasma levels of diltiazem achieved in this study.

Diltiazem and verapamil affected isoproterenol dose-response curves in a qualitatively similar fashion. The noncompetitive nature of the interference by either of these drugs with the effects of a β -adrenergic agonist at myocardial β -receptors presumably results from the fact that calcium channel blockers interfere not with the β -receptors themselves, but with the membrane calcium channels "opened" by β -adrenergic activation that contribute to improved conduction and contractility (2). The curves from low and high verapamil and high diltiazem were nearly identical, whereas the lower plasma levels of diltiazem in this study caused less flattening of the heart rate response curve. A dose-response relationship was apparent with the doses of diltiazem used, whereas with verapamil both dose levels depressed the curve to a similar extent.

The pentobarbital-anesthetized dog, although providing a stable background against which drug interactions could be studied, is unlike the awake subject or one anesthetized with other agents, such as narcotics or the inhalational anesthetics. Although it affords stability for extended periods of time, especially when given by continuous infusion (14), pentobarbital has its own effects on conduction, atrioventricular nodal refractoriness, HR, blood pressure, and autonomic reflex tone. Previous studies have attributed the relative hypertension and tachycardia ob-

served during pentobarbital anesthesia to vagal withdrawal and/or increased adrenergic activity (15). Low levels of plasma NE and EPI in the control dogs, plus the fact that relatively minor hemodynamic effects resulted from the addition of propranolol alone to the group II dogs, suggest that pentobarbital resulted primarily in vagal withdrawal in our animals. Adrenergic activation occurred subsequently as a response to the calcium channel blockers. The compensatory response to calcium channel blockers, with or without concomitant β -adrenergic blockers, may be modified in an animal, either in the awake state, or when anesthetized with agents with different effects on the autonomic nervous system. Furthermore, the balance of autonomic control is variable among disease states as well as among anesthetic states. Individuals with compromised left ventricular function (i.e., decreased adrenergic sensitivity (16) with dependence on a high level of sympathetic tone for hemodynamic homeostasis may be more sensitive to the combination of calcium channel blockers and β -adrenergic blockade (17). The effects of propranolol are known to be dependent on the preexisting level of sympathetic tone; in a milieu of low sympathetic activity, the apparent effect is very small, whereas with high activity β -adrenergic blockade results in myocardial depression (18).

Diltiazem and verapamil were given in equivalent bolus doses followed by similar infusion rates. The absolute values for the plasma diltiazem levels were lower than those of verapamil. Although these plasma levels for both verapamil and diltiazem fall within those which are considered therapeutic in man, and the PR interval, a marker of the pharmacodynamic effect of verapamil and diltiazem, was prolonged with low and high verapamil and high diltiazem, parallel comparisons between diltiazem and verapamil at the low and high doses used in this study may not be valid. Kates et al. (19) found that there was a discrepancy in the absolute plasma levels of verapamil or diltiazem needed to achieve an equivalent level of hypotension in halothane-anesthetized swine. To achieve a 25-30% decrease in MAP below control levels during halothane anesthesia in swine, the plasma verapamil levels needed were 310 ± 33 ng/mL, whereas the plasma diltiazem levels required were 1651 ± 139 ng/mL. It is possible that, at higher plasma levels of diltiazem attained through different dosages, the hemodynamic profiles of the two drugs may have been more similar in combination with propranolol in dogs. We cannot say from these data that diltiazem, *per se*, is a safer drug to use in combination with propranolol; it may be just a matter of the dose given.

Hamann et al. (20), who studied the combined ef-

fects of propranolol with verapamil in pentobarbital-anesthetized dogs, found that during the coadministration of the two, plasma levels of verapamil increased, perhaps secondary to decreased hepatic clearance. In the present study there was no statistical difference between verapamil levels in group VI compared to those in group IV during period 3 or, using values for only the group VI animals able to complete period 4, during period 4. The result of the study by Hamann et al. confirmed that severe cardiovascular consequences may occur with the combination of verapamil and propranolol (20). Those investigators did not evaluate adrenergic responsiveness.

The results of the present study emphasize the importance of an intact autonomic nervous system that can respond with reflex sympathetic activation to compensate for the effects of calcium channel blockers. The combination of a calcium channel blocker with propranolol to treat tachycardia may result in decreased cardiac performance and increased peripheral vascular resistance, a most undesirable combination. The deleterious potential of impairing β -adrenergic function in the presence of a calcium channel blocker was particularly apparent with the higher levels of verapamil tested in this study. The higher levels of verapamil were well-tolerated alone, yet in the presence of β -adrenergic blockade they caused second degree or higher heart block in 6 of 9 animals and hemodynamic collapse in half of those. These results indicate that the less a subject is able to generate a compensatory autonomic response, either on the basis of pharmacologic interference or a preexisting disease state, the greater the susceptibility to the negative cardiovascular effects of calcium channel blockers. The response to exogenously administered β -agonists was also decreased, and orders of magnitude larger doses of isoproterenol may be required to cause an equivalent increase in heart rate in the presence of a combined blockade compared to that required in the presence of an anesthetic alone.

The authors thank Marion Laboratories, Inc. for supplying the diltiazem, Knoll Pharmaceutical Co. for supplying the verapamil, Owen Buchea and Thomas Patin for technical assistance, and Tony Law and Ellen Provost for performing the plasma assays.

References

1. Fleckenstein A. Specific pharmacology of calcium in myocardium, cardiac pacemakers, and vascular smooth muscle. *Ann Rev Pharmacol Toxicol* 1977;17:149-66.
2. Lindenmann JP, Bailey JC, Watanabe AM. Potential biochemical mechanisms for regulation of the slow inward current: theoretical basis for drug action. *Am Heart J* 1982;103:746-56.
3. Bala Subramanian V, Bowles MJ, Davies AB, Raftery EB. Combined therapy with verapamil and propranolol in chronic stable angina. *Am J Cardiol* 1982;49:125-32.
4. Leon MB, Rosing DR, Bonow RO, Lipson LC, Epstein SE. Clinical efficacy of verapamil alone and combined with propranolol in treating patients with chronic stable angina pectoris. *Am J Cardiol* 1981;48:131-9.
5. Strauss WE, Parisi AF. Superiority of combined diltiazem and propranolol therapy for angina pectoris. *Circulation* 1985;71:951-7.
6. Benaim ME. Asystole after verapamil. *Br Med J* 1972;2:169-70.
7. Boothby CB, Garrard CS, Pickering D. Verapamil in cardiac arrhythmias. *Br Med J* 1972;2:349.
8. Lievre M, Descotes J, Faucon G. Interaction of diltiazem with propranolol on atrioventricular conduction and refractoriness in the dog. *Experientia* 1982;38:1407-8.
9. Watson E, Kapur PA. High performance liquid chromatographic determination of verapamil in plasma by fluorescence detection. *J Pharm Sci* 1981;70:800-1.
10. Verghese C, Smith MS, Aanonsen L, Pritchett ELC, Shand DG. High performance liquid chromatographic analysis of diltiazem and its metabolite in plasma. *J Chromatog* 1983;272:149-55.
11. Watson E. Liquid chromatography with electrochemical detection for plasma norepinephrine and epinephrine. *Life Sci* 1981;28:493-7.
12. Mullane JF, Kaufman J, Dvornik D, Coelho J. Propranolol dosage, plasma concentration, and beta blockade. *Clin Pharmacol Ther* 1982;32:692-700.
13. Davis DD, Temte JV. Effects of propranolol on the transmembrane potentials of ventricular muscle and Purkinje fibers of the dog. *Circ Res* 1968;22:661-77.
14. Hotvedt R, Platou ES, Koppang ER, Refsum H. Pentobarbital plasma concentrations and cardiac electrophysiology during prolonged pentobarbital infusion anaesthesia in the dog. *Acta Anaesthesiol Scand* 1982;26:638-42.
15. Manders WT, Vatner SF. Effects of sodium pentobarbital on left ventricular function and distribution of cardiac output in dogs with particular reference to the mechanism for tachycardia. *Circ Res* 1976;39:512-7.
16. Bristow MR, Ginsburg R, Minobe W, et al. Decreased catecholamine sensitivity and beta-adrenergic-receptor density in failing human hearts. *N Engl J Med* 1982;307:205-11.
17. Chew CYC, Hecht HS, Collett JT, McAllister RG, Singh BN. Influence of the severity of ventricular dysfunction on hemodynamic responses to intravenously administered verapamil in ischemic heart disease. *Am J Cardiol* 1981;47:917-22.
18. Shand DG. Propranolol. *N Engl J Med* 1975;293:280-5.
19. Kates RA, Zaggy AP, Norfleet EA, Heath KR. Comparative cardiovascular effects of verapamil, nifedipine, and diltiazem during halothane anesthesia in swine. *Anesthesiology* 1984;61:10-8.
20. Hamann SR, Kaltenborn KE, Vore M, Tan TG, McAllister RG Jr. Cardiovascular and pharmacokinetic consequences of combined administration of verapamil and propranolol in dogs. *Am J Cardiol* 1985;56:147-56.

Comparative Toxicity of Atracurium and Metocurine in Isolated Rat Hepatocytes

Vladimir Nigrovic, MD, James E. Klaunig, PhD, Sarah L. Smith, MA,
Norman E. Schultz, BS, and Aron Wajskol, MD

NIGROVIC V, KLAUNIG JE, SMITH SL, SCHULTZ NE, WAJSKOL A. Comparative toxicity of atracurium and metocurine in isolated rat hepatocytes. *Anesth Analg* 1986;65:1107-11.

Primary cultures of liver cells isolated from seven rats were used to study the possible toxicity of atracurium and metocurine. The muscle relaxants were separately added to the culture medium and the cells then incubated for 4 hr. The amount of lactic dehydrogenase (LDH) that leaked into the culture medium was determined at the end of incubation. The customary assumption was made that the exudation of LDH reflects the toxic effects of the relaxants. In untreated dishes, approximately 11% of the total intracellular LDH leaked out during the incubation. The net leakage of LDH produced by the relaxants was obtained by subtracting this

amount from the LDH activity determined in the media of dishes with the relaxants added. On this basis, metocurine, in concentrations of $12-850 \times 10^{-6}M$, did not cause a net leak of LDH. On the other hand, atracurium, in similar molar concentrations, caused a statistically significant and concentration-dependent leak of LDH that, at its maximum, amounted to more than one half of the intracellular LDH. The results are interpreted in terms of damage to cellular membranes produced by atracurium or its metabolites. Although the exact biochemical process was not identified, we hypothesize that acrylates—produced by Hofmann elimination from atracurium—might be the likely toxic species.

Key Words: TOXICITY—atracurium, metocurine. NEUROMUSCULAR RELAXANTS—atracurium, metocurine.

Due to its unique degradation pathway (1), atracurium has inspired a great deal of experimental and clinical interest before and after its recent introduction into clinical practice as a muscle relaxant with an intermediate duration of action. As a result, much has been learned about its mode of action (2,3) and ease of reversal (4), its pharmacodynamic profile in healthy patients (5-9) and in patients with organ failures (10-13), and about its pharmacokinetic parameters in humans (14-16). The plethora of published reports dealing with these topics contrasts with the paucity of published information regarding its potential for causing adverse reactions. Except for several clinical reports on undesired effects (17-24), we know of only one published report on evaluation of possible toxic side-effects of atracurium. It concludes that "no important toxic actions were found in three species" (25). Similarly, no fetotoxic, teratogenic nor mutagenic effects (Ames test) were found (25).

The novel degradation and inactivation pathway of atracurium, in chemical terms an "elimination" reaction (1), causes a break of the bond between the quaternary nitrogen and the adjacent carbon atom in the aliphatic chain. The two products, laudanosine and an acrylate, are produced in equimolar amounts, and yet the toxicologic studies have been conducted with unequal emphasis placed on the two metabolites. After exposure to atracurium, laudanosine has been searched for and detected in experimental animals (26) and in plasma of both normal patients and patients in renal failure (27). The compound's known effect on the central nervous system of experimental animals (28,29) has been recently confirmed (30) and an apparent lightening of anesthesia implicated (31). Miller et al. (32) concluded that the administration of atracurium in recommended doses is very unlikely to produce toxic plasma levels of laudanosine. In contrast except for a brief, theoretical note (33) expressing concern about potential adverse effects of acrylates generated in vivo from atracurium, no information is available concerning either the fate of acrylates in vivo or the biochemical interactions likely to result from their presence in the organism. Even the chemical nature of acrylates formed in vivo is not known:

Received from the Departments of Anesthesiology, Pathology, and Pharmacology, Medical College of Ohio, Toledo, Ohio. Accepted for publication June 5, 1986.

Address correspondence to Dr. Nigrovic, Department of Anesthesiology, Medical College of Ohio, Toledo, OH 43699.

whereas early reports suggest formation of penta-methylene diacrylate (5), later ones suggest the formation of other acrylate moieties (26). Experimentally only the "quaternary monoacrylate" has been detected in small amounts in the bile and urine of two cats (26). There are no reports on plasma concentrations of acrylates associated with the intravenous (IV) administration of atracurium in humans or in experimental animals. Thus the *in vivo* fate of the aliphatic chain of atracurium (the parent moiety for acrylates) remains unknown. However, ester bonds in the chain were postulated to undergo hydrolysis (34). The products of ester hydrolysis are generally presumed to be nontoxic.

Acrylates, characterized by the α,β -unsaturated carbonyl group, show high reactivity toward nucleophiles and hence may covalently bind to (i.e., alkylate) many such endogenous compounds. The *in vivo* consequences of this reaction depend on the concentration of acrylates, their chemical reactivity, and the functional role of the endogenous nucleophiles, as well as on the biologic defense and repair mechanisms available for restitution. Taking into account the difficulties involved in testing for chronic toxicity of muscle relaxants (25), it is not surprising that no adverse effects were found during the routine preclinical testing of atracurium.

Based on the presumption that atracurium—a bisquaternary ion—is distributed predominantly in the extracellular space and thus comes in contact with the outside of the cell membranes, we decided to examine the effects of atracurium on the integrity of cellular membranes in the primary culture of rat hepatocytes. In this system, damage to cell membranes becomes manifest by exudation of the intracellular enzymes into the culture (i.e., extracellular) medium (35). In the present experiments, we selected lactic dehydrogenase (LDH) as the marker for intracellular enzymes. Identical experiments were conducted either with atracurium or metocurine in the culture medium. We selected metocurine because of its bisquaternary nature, its chemical similarity to atracurium (36), and its metabolic inertness *in vivo*.

Methods and Materials

Rat hepatocytes were isolated and cultured as described by Klaunig et al. (37,38). Briefly, male rats (Wistar strain, 220–270 g) were anesthetized by intraperitoneal administration of sodium pentobarbital (65 mg/kg). The abdominal cavity was opened and the liver perfused via the portal vein first with Hank's solution containing EGTA (ethylene glycol bis(β -aminoethyl ether) N,N,N',N'-tetracetic acid, 0.19 mg/ml)

and immediately thereafter with L-15 medium (Gibco Laboratory, Grand Island, NY) containing collagenase (type IV, 220 U/ml). Liver cells were separated using combing and repetitive pipetting. One million viable cells (viability, estimated by trypan blue exclusion, was better than 85%) were placed onto each culture dish (60 mm diameter) in 3 ml of L-15 culture medium supplemented with the following: dexamethasone (10^{-6} M), insulin (0.024 U/ml), glucose (1 mg/ml), gentamicin (0.025 mg/ml), and 10% fetal bovine serum (Hy Clone, Logan, UT). Cells were allowed to attach for 2.5 hr in an incubator (37°C, air atmosphere, 100% relative humidity). After attachment, the medium was discarded and the cells were washed once with L-15 medium. Fresh L-15 culture medium was then added. Volumes of atracurium or metocurine were added to each dish sufficient to produce the desired molar concentrations of the relaxant in a total volume of 5 ml. Each concentration of each muscle relaxant was tested in three dishes. A total of seven experiments was performed. Incubation medium without muscle relaxants (5 ml) was added to six additional dishes in each experiment. Three of the dishes served for determination of enzyme release with no treatment ("control"), and the remaining three were treated with a detergent (50 μ l of Triton X-100) at the end of incubation to produce a complete lysis of the cells. Incubation (at 37°C, air atmosphere, 100% humidity) was carried out for 4 hr after the addition of the relaxants, at which time the incubation medium was removed for spectrophotometric determination of LDH activity (Beckman Multistat Autoanalyzer). The presence of Triton X-100, atracurium, or metocurine in culture medium did not influence the measurement of LDH activity. All chemicals, except those specified, were obtained from Sigma Chemical Co., St. Louis, MO.

Commercial solutions of atracurium (Tracrium, Burroughs Wellcome Co., Research Triangle Park, NC) were used throughout. In order to obtain the required molar concentrations of metocurine, the commercial solution (Metubine, Eli Lilly and Co., Indianapolis, IN) was concentrated four-fold (to 8 mg/ml) by blowing dry nitrogen gas over the solution of metocurine at room temperature. In separate tests it was ascertained that the concentrating procedure did not influence either the potency of metocurine as a muscle relaxant (rat sciatic nerve-m. gastrocnemius preparation) or its effect on the isolated hepatocytes (data not presented). Molecular weights of atracurium besylate and metocurine iodide were assumed to be 1243.49 and 906.03, respectively.

Leakage of LDH was quantified as follows: LDH activity present in the culture medium was subtracted

Table 1. Release of Intracellular LDH by Rat Hepatocytes during Incubation (4 hr) with Atracurium and Metocurine^a

		Concentration of atracurium (10^{-5} M)							Concentration of metocurine ^b (10^{-6} M)				
		8.06	25.5	80.6	254.8	438.7	622.6	806.5	11.9	35.3	111.1	352.9	851.1
% LDH released ^b	Mean	3.83	5.28	8.55	16.9	30.4	47.6	57.5	1.38	0.72	0.86	0.52	1.01
	SEM ^c	0.68	0.57	1.14	2.9	5.6	6.1	6.4	0.78	0.69	0.75	0.79	0.79

^aEach concentration was tested in 21 culture dishes (three dishes from each of the seven animals).^bExpressed in percent of LDH activity remaining in untreated cells at the end of 4 hr of incubation.^cLDH leak at all concentrations of atracurium was highly significant ($P < 0.01$).

from the activity determined in dishes containing cells lysed by the detergent and the difference set to 100%. This value represents the maximally releasable amount of LDH. Enzyme activity present in the incubation medium in the three untreated dishes was averaged. This activity was subtracted from the activity present in the medium of each treated dish and the difference expressed in percent of the maximally releasable enzyme activity.

The data were analyzed using the analysis of variance. No transformation was utilized, because the indicated logarithmic transformation would not have been possible with approximately one half of the metocurine data (negative values). In addition, a non-parametric enumeration analysis was performed. A χ^2 -test was applied to a 2×2 contingency table constructed by counting the dishes exposed to either atracurium or metocurine that showed LDH activity either above or below that found in the corresponding untreated (control) dishes. All data are presented as mean \pm SEM.

Results

The pH of the L-15 culture medium was 7.4; this value did not change with the addition of the relaxants or with incubation. Data from all seven rats are summarized in Table 1. On the average, in dishes with no relaxant added, $10.4 \pm 1.5\%$ of the intracellular LDH exuded into the culture medium during the 4-hr incubation period. Atracurium caused an additional net leak of LDH even in the lowest concentration tested (8×10^{-6} M). As the concentration of atracurium increased, the leak became more pronounced. More than half of the intracellular LDH leaked out when atracurium concentration reached 8×10^{-4} M. In contrast to these findings, metocurine caused no reproducible leak of LDH into the medium when tested over a similar range of molar concentrations.

The results of the enumeration analysis support the above quantitative findings. Out of a total of 147 dishes treated with atracurium (seven animals \times seven concentrations in triplicate), the activity of LDH in

only one atracurium dish was lower than the activity in the untreated, control dishes. The sole dish was one of the 21 dishes treated with the lowest concentration of atracurium. With metocurine, on the other hand, out of the total of 105 observations (seven animals \times five concentrations in triplicate), 49 showed the enzymatic activity just above and 56 showed the activity just below those in respective control (untreated) dishes.

Statistical analysis showed that the enzyme leakage produced by various doses of atracurium was very unlikely to have arisen by a chance observation ($P < 0.001$). The probability, on the other hand, that metocurine produced a net leak of LDH did not rise above that of a chance observation ($P > 0.2$). The enumeration analysis indicated that the difference in the frequency of a net enzyme leak between the dishes incubated with atracurium or metocurine was unlikely to have occurred by chance ($\chi^2 = 97.04$; $P < 0.01$).

Discussion

The present experiments represent the first attempt to determine whether muscle relaxants exert toxic effects on isolated hepatocytes. The applied technique is a relatively crude test for determining the integrity of cellular membranes under in vitro conditions (35). Because no previous data were available for comparison, it was necessary to include in the study a clinically well-known relaxant. Metocurine was selected because of its chemical similarity to atracurium, its bisquaternary structure, its stability in vivo, and its clinical innocuousness with regard to liver toxicity. The lack of any measurable effect of metocurine on the transmembrane leakage of the intracellular enzyme LDH was therefore expected and, indeed, was experimentally confirmed. These negative results contrast sharply with those obtained with the new muscle relaxant, atracurium. Release of LDH during the 4 hr of incubation of rat hepatocytes with atracurium was evident even with the lowest concentration tested. Moreover, the effect was positively correlated with the concentration of atracurium in the

culture medium. The contrast between the lack of effects of metocurine on one hand, and the net leakage of LDH produced by atracurium on the other, permits the conclusion that atracurium causes exudation of intracellular enzymes. It is generally assumed (35) that the leak is due to the loss of the structural integrity of the cellular membrane.

The events leading to this change in membrane permeability to LDH cannot be deduced from these initial experiments. The possibility has to be considered that the additives in the commercial preparation of atracurium, atracurium itself, and/or any one of the postulated metabolites may be responsible. We suspect that acrylates generated from atracurium—rather than the parent compound—are responsible. If, as previously postulated, acrylates are generated from atracurium and, due to their chemical reactivity, alkylate endogenous nucleophiles in contact with the extracellular space (33), the cellular membrane will probably be the first structure attacked. Subsequent alteration of the membrane would permit exudation of the intracellular enzymes. Although likely, this explanation requires further verification. A detailed examination of the effects of each of the postulated metabolites on the membrane integrity is strongly indicated.

Inevitably, the question arises as to the relevance of the tested concentrations of atracurium relative to those expected under in vivo conditions. There are no reports either on the distribution of atracurium or on its concentrations in various organs after intravenous administration. Two sets of data may be consulted to partially resolve the issue: First, after an intubating dose of atracurium (0.5 mg/kg IV), plasma concentrations decline rapidly and reach approximately 1×10^{-6} M 30 min after the injection (11,12,14,15,26,39). Obviously, the plasma concentrations are higher than this value at shorter time intervals and progressively decrease later on. Second, although organ concentrations of atracurium have not been determined, in vitro experiments have estimated the concentration of atracurium required to produce neuromuscular blockade. Amaki et al. (40), for example, found that a $0.186 \pm 0.008 \times 10^{-6}$ M concentration of atracurium is required to halve the indirectly elicited twitch of the lumbrical muscle from the guinea pig. In the diaphragm-phrenic nerve preparation of the guinea pig (41), a 1×10^{-6} M concentration of atracurium is needed to produce a 50% reduction of the muscle twitch in response to indirect stimulation of the phrenic nerve by single stimuli. A ten-fold higher concentration completely abolished the muscle twitch. In a computer model of the pharmacokinetic and pharmacodynamic responses to atracurium in cats,

Weatherley et al. (14) projected that within 10 min after an intravenous injection of a small dose of atracurium (0.3 mg/kg), its concentration in the effector compartment may reach $2\text{--}2.5 \times 10^{-6}$ M, a concentration sufficient to cause complete suppression of the tetanic response. Taken together, these data suggest that after an intubating dose of atracurium, the concentration of atracurium in various organs during the period of total muscle paralysis may be at least in the micromolar range. We elected to examine a higher range of concentrations for evidence of toxic effects. Our data show that even at the lowest concentration utilized in this study (8×10^{-6} M), atracurium produced leakage of an intracellular enzyme.

No toxic effects of atracurium in vivo were reported in the one toxicologic study published thus far (25). A letter (42) cites unpublished results in support of a similar claim. Our results clearly stand in contrast to these older data. The likely explanation may be found in the conduct of the tests. Whereas the older data represent routine laboratory studies, the present study was targeted and conducted with a specific question in mind. The possibility remains, however, that the intact organism may repair any damage caused by atracurium or its metabolites whereas a similar repair under in vitro conditions may not occur.

One final consideration adds a factor of uncertainty to any attempt to translate the present data into a clinical context. If, as previously reported, atracurium is degraded very rapidly in rats via enzyme-catalyzed hydrolysis (43), then it follows that the cell damage caused by a postulated product of the elimination reaction (Hofmann) may be different in species (including humans) (44) with lower rates of enzyme-catalyzed hydrolysis. This possibility and others will be examined in future experiments.

V. Nigrovic received the 1986 B. B. Sankey Anesthesia Advancement Award from the International Anesthesia Research Society. Support from this Award and from the intramural funds of the Department of Anesthesiology, Medical College of Ohio, are gratefully acknowledged. Mrs. Jacalynn Hakius provided excellent secretarial help.

References

1. Stenlake JB, Waigh RD, Dewar GH, Hughes R, Chappel DJ, Coker GG. Biodegradable neuromuscular blocking agents. Part 4. Atracurium besylate and related polyalkylene di-esters. *Eur J Med Chem* 1981;16:515-24.
2. Hughes R, Chappel DJ. The pharmacology of atracurium: a new competitive neuromuscular blocking agent. *Br J Anaesth* 1981;53:31-44.
3. Coker GG, Dewar GH, Hughes R, Hunt TM, Payne JP, Stenlake JB, Waigh RD. A preliminary assessment of atracurium, a new

- competitive neuromuscular blocking agent. *Acta Anaesthesiol Scand* 1981;25:67-9.
4. Jones RM, Pearce AC, Williams JP. Recovery characteristics following antagonism of atracurium with neostigmine and edrophonium. *Br J Anaesth* 1984;56:453-7.
 5. Payne JP, Hughes R. Evaluation of atracurium in anaesthetized man. *Br J Anaesth* 1981;53:45-54.
 6. Basta SJ, Ali HH, Savarese JJ, Sunder N, Gionfriddo M, Cloutier G, Lineberry C, Cato AE. Clinical pharmacology of atracurium besylate (BW33A): a new non-depolarizing muscle relaxant. *Anesth Analg* 1982;61:723-9.
 7. Pearce AC, Williams JP, Jones RM. Atracurium for short surgical procedures in day patients. *Br J Anaesth* 1984;56:973-6.
 8. Scott RPF, Goat VA. Atracurium: its speed of onset. A comparison with suxamethonium. *Br J Anaesth* 1982;54:909-11.
 9. Katz RL, Stirt J, Murray AL, Lee C. Neuromuscular effects of atracurium in man. *Anesth Analg* 1982;61:730-4.
 10. Hunter JM, Jones RS, Utting JE. Use of atracurium in patients with no renal function. *Br J Anaesth* 1982;54:1251-8.
 11. Hunter JM, Jones RS, Utting JE. Comparison of vecuronium, atracurium and tubocurarine in normal patients and in patients with no renal function. *Br J Anaesth* 1984;56:941-52.
 12. Ward S, Neill EAM. Pharmacokinetics of atracurium in acute hepatic failure (with acute renal failure). *Br J Anaesth* 1983;55:1169-72.
 13. Fahey MR, Rupp SM, Fisher DM, Miller RD, Sharma M, Canfell C, Castagnoli K, Hennis PJ. The pharmacokinetics and pharmacodynamics of atracurium in patients with and without renal failure. *Anesthesiology* 1984;61:699-702.
 14. Weatherley BC, Williams SG, Neill EAM. Pharmacokinetics, pharmacodynamics and dose-response relationships of atracurium administered i.v. *Br J Anaesth* 1983;55:395-455.
 15. Ward S, Neill EAM, Weatherley BC, Corall IM. Pharmacokinetics of atracurium besylate in healthy patients (after a single i.v. bolus dose). *Br J Anaesth* 1983;55:113-8.
 16. Fisher DM, Canfell C, Fahey MR, Rosen JI, Rupp SM, Sheiner LB, Miller RD. Elimination of atracurium in humans: contribution of Hofmann elimination and ester hydrolysis. *Anesthesiology* 1985;63:A310.
 17. McHutchon A, Lawler PG. Bradycardia following atracurium. *Anaesthesia* 1983;38:597-8.
 18. Sale JP. Bronchospasm following the use of atracurium. *Anaesthesia* 1983;38:511-2.
 19. Mirakhur RK, Lyons SM, Carson IW, Clarke RSJ, Ferres CJ, Dundee JW. Cutaneous reaction after atracurium. *Anaesthesia* 1983;38:818-9.
 20. Carter ML. Bradycardia after the use of atracurium. *Br Med J* 1983;287:247-8.
 21. Basta SJ, Savarese JJ, Ali HH, Moss J, Gionfriddo M. Histamine-releasing potencies of atracurium, dimethyl tubocurarine and tubocurarine. *Br J Anaesth* 1983;55:1055-106S.
 22. Mercer JD. A severe anaphylactic reaction to atracurium. *Anaesth Intens Care* 1984;12:262-9.
 23. Srivastava S. Angioneurotic oedema following atracurium. *Br J Anaesth* 1984;56:932.
 24. Friddy R. Bradycardia after atracurium. *Anaesth Intens Care* 1984;12:175.
 25. Skarpa M, Dayan AD, Follenfant M, James DA, Moore WB, Thomson PM, Lucke JN, Morgan M, Lovell R, Medd R. Toxicity testing of atracurium. *Br J Anaesth* 1983;55:275-295.
 26. Neill EAM, Chapple DJ. Metabolic studies in the cat with atracurium: a neuromuscular blocking agent designed for non-enzymic inactivation at physiologic pH. *Xenobiotica* 1982;12:203-10.
 27. Fahey MR, Rupp SM, Canfell C, Fisher DM, Miller RD, Sharma M, Castagnoli K, Hennis PJ. Effect of renal failure on laudanosine excretion in man. *Br J Anaesth* 1985;57:1049-51.
 28. Eabel A. Etude comparative de la laudanosine et de la papaverine du point de vue pharmacodynamique. *Rev Med Suisse Romande* 1899;19:657-68.
 29. Mercier J, Mercier E. Action de quelques alcaloïdes secondaires de l'opium sur l'électrocorticogramme du chien. *C R Soc Biol* 1955;149:760-2.
 30. Hennis PJ, Fahey MR, Miller RD, Canfell C, Shi WZ. Pharmacology of laudanosine in dogs. *Anesthesiology* 1984;61:A305.
 31. Shi W-Z, Fahey MR, Fisher DM, Miller RD, Canfell C, Eger EI. Laudanosine (a metabolite of atracurium) increases the minimum alveolar concentration of halothane in rabbits. *Anesthesiology* 1985;63:584-8.
 32. Miller RD, Rupp SM, Fisher DM, Cronelly R, Fahey MR, Sohn YJ. Clinical pharmacology of vecuronium and atracurium. *Anesthesiology* 1984;61:444-53.
 33. Nigrovic V, Koechel DA. Atracurium—additional information needed. *Anesthesiology* 1984;60:606-7.
 34. Merrett RA, Thompson CW, Webb FW. In vitro degradation of atracurium in human plasma. *Br J Anaesth* 1983;55:61-6.
 35. Solinna EM. Isolation and culture of liver cells and their use in the biochemical research of xenobiotics. *Med Biol* 1982;60:237-54.
 36. Bowman WC. New neuromuscular blocking drugs in anaesthetic practice. *Pharm Internat* 1983;4:131-4.
 37. Kaunig JE, Goldblatt PJ, Hinton DE, Lipsky MM, Chacko J, Trump BF. Mouse liver cell culture. I. Hepatocyte isolation. *In Vitro* 1981;17:913-25.
 38. Kaunig JE, Goldblatt PJ, Hinton DE, Lipsky MM, Chacko J, Trump BF. Mouse liver cell culture. II. Hepatocyte isolation. *In Vitro* 1981;17:926-34.
 39. Sailer RL, Brandom BW, Cook DR. Determination of atracurium in plasma by high-performance liquid chromatography. *Anesth Analg* 1985;64:58-62.
 40. Anaki Y, Waud BE, Waud DR. Atracurium—receptor kinetics: simple behavior from a mixture. *Anesth Analg* 1985;64:777-80.
 41. Healy TEJ, Palmer JP. In vitro comparison between the neuromuscular and ganglionic blocking potency ratios of atracurium and tubocurarine. *Br J Anaesth* 1982;54:1307-11.
 42. Cato AE, Lineberry CG, Macklin AW. Concerning toxicity testing of atracurium. *Anesthesiology* 1985;62:94-5.
 43. Nigrovic V, Auen M, Wajskol A. Enzymatic hydrolysis of atracurium in vivo. *Anesthesiology* 1985;62:606-9.
 44. Nigrovic V, Pandya JB, Auen M, Wajskol A. Inactivation of atracurium in human and rat plasma. *Anesth Analg* 1985;64:1047-52.

Preoperative Oral Fluids: Is a Five-hour Fast Justified Prior to Elective Surgery?

J. Roger Maltby, MB, BChir, FFARCS, FRCPC, A. D. Sutherland, MB, BS, FFARCS,
J. P. Sale, BSc, MB, FFARCS, and E. A. Shaffer, FRCPC

MALTBY JR, SUTHERLAND AD, SALE JP, SHAFFER EA.
Preoperative oral fluids: is a five-hour fast justified prior
to elective surgery? *Anesth Analg* 1986;65:1112-6.

The effects of preoperative oral administration of 150 ml fluid were studied prospectively in 140 unpremedicated, ambulatory outpatients presenting for first trimester therapeutic abortion. Intraoperative gastric fluid volume, pH, and rate of gastric emptying were measured in the four groups to which patients were randomly assigned. At an average time of 2½ hr preoperatively all patients received either oral ranitidine, 150 mg, or a placebo tablet, with the nonabsorbable marker dye bromosulphthalein (BSP), 50 mg in 10 ml water, followed by either 150 ml water or no further fluid. The effect of volume ingested was assessed by comparing the volume of gastric contents obtained by gastric tube suctioning at the completion of surgery in the two groups given placebos. The gastric volume was significantly

less in patients given 150 ml water (17.6 ± 14.5) than in those given only BSP (26.7 ± 18.9) ($P < 0.02$), and was further significantly decreased in the two groups given ranitidine (8.3 ± 7.3 , 9.5 ± 7.7 ml) ($P < 0.001$). Mean pH values were significantly higher in the two ranitidine groups (5.52 ± 1.79 , 5.03 ± 1.79) than in the two placebo groups (1.75 ± 0.94 , 1.92 ± 1.27). The combination of a residual volume of 25 ml and pH less than 2.5 was found in 46% of patients given only BSP with placebo, in 23% of those given 150 ml water with placebo, and in no patient given ranitidine. There was no correlation between the gastric volume or pH values with the ingestion-surgery interval in patients given 150 ml water.

Key Words: GASTROINTESTINAL TRACT—gastric emptying. HISTAMINE—ranitidine. ANESTHESIA—outpatient.

"While a complete emptying of the stomach can never be guaranteed, a minimum of five hours (preoperative starvation) in the absence of pain, trauma, apprehension, narcotics, gastrointestinal disorders, or premedications is suggested except under emergency conditions" (1). Such guidelines have been followed in most hospitals for many years. Foods pass through the stomach at variable and somewhat unpredictable rates, sometimes taking up to 12 hr (2,3). In contrast, water and crystalloid-containing fluids have a 50% emptying time of only 12 min (4). It therefore appears illogical to have a single guideline for both preoperative solids and liquids.

Prolonged preoperative starvation causes patient discomfort, yet more than one third of fasting patients have a gastric volume greater than 25 ml, and in 90% the gastric fluid pH is less than 2.5 (5). Previous

studies have shown that H₂ receptor antagonists favorably alter preoperative gastric volume and pH (5-7).

In view of the difference in physiologic handling of liquids and solids by the gastrointestinal tract, it was decided to assess the safety and effects of ingesting 150 ml water. This amount of fluid was ingested 120-180 min before induction of anesthesia, together with either oral ranitidine or placebo, in outpatients presenting for first trimester abortion. This group of patients may be at higher risk of acid aspiration because of the purported association of pregnancy with delayed gastric emptying (8).

Methods

After approval of the study protocol by the University of Calgary Joint Ethics Committee and with informed consent, 140 ambulatory patients presenting for first trimester therapeutic abortion were studied. Details of the patients' age, weight, gestation, smoking history, fasting interval, and history of recent vomiting or symptoms of reflux were recorded on admission to the daycare holding area. Hunger and thirst were

Received from the Departments of Anaesthesia and Medicine, Foothills Hospital at the University of Calgary, Calgary, Alberta, Canada. Accepted for publication June 2, 1986.

Address correspondence to Dr. Maltby, Department of Anaesthesia, Foothills Hospital at the University of Calgary, 1403 29th Street N.W., Calgary, Alberta, Canada T2N 2T9.

Table 1. Patient Characteristics (mean \pm SD)

	<i>n</i>	Age (yr)	Weight (kg)	Gestation (weeks)	Duration of fasting (hr)	Ingestion-surgery interval (min)
Group 1 (P + 150 ml)	35	24.5 \pm 4.4	58.8 \pm 9.2	8.9 \pm 1.5	14.4 \pm 2.1	144 \pm 17
Group 2 (R + 150 ml)	35	24.4 \pm 4.3	61.5 \pm 8.7	9.3 \pm 2.0	13.9 \pm 2.3	145 \pm 19
Group 3 (P)	35	24.9 \pm 5.1	58.9 \pm 8.5	9.4 \pm 1.7	14.1 \pm 1.6	150 \pm 19
Group 4 (R)	35	24.9 \pm 4.1	59.3 \pm 8.9	9.4 \pm 1.5	14.0 \pm 1.4	145 \pm 16

P, Placebo; R, Ranitidine.

Table 2. Gastric Volume and pH and Percentage of Dye Recovered

	Volume ^a	pH ^a	% Dye recovered ^a
Group 1 (150 ml water + placebo) (<i>n</i> = 35)	17.6 \pm 14.5 ^b (0-56)	1.75 \pm 0.94 (0.75-6.5) <i>n</i> = 33	0
Group 2 (150 ml water + ranitidine) (<i>n</i> = 35)	8.3 \pm 7.5 ^c (0-24)	5.52 \pm 1.79 ^c (1.33-7.71) <i>n</i> = 28	0.008 \pm 0.019 (0-0.080)
Group 3 (10 ml water + placebo) (<i>n</i> = 35)	26.7 \pm 18.9 (0-80)	1.92 \pm 1.27 (0.91-6.44) <i>n</i> = 33	0.002 \pm 0.019 (0-0.05)
Group 4 (10 ml water + ranitidine) (<i>n</i> = 35)	9.5 \pm 7.7 ^c (0-35)	5.03 \pm 1.79 ^c (1.64-7.51) <i>n</i> = 31	0.004 \pm 0.015 (0-0.09)

The differences between numbers in which pH was measured and numbers per group represents patients with no gastric aspirate.

^aMean \pm SD (Range)^b*P* < 0.02 vs group 3.^c*P* < 0.01 vs groups 1 and 3.

graded—nil, mild, moderate, extreme—on admission and again on arrival in the operating room. All patients had fasted for at least 10 hr from midnight until arrival at the hospital. Those receiving any medication known to affect gastric secretion were excluded. No sedative or narcotic drug premedication was given. Between 120 and 180 min preoperatively, all patients were given bromosulphthalein (BSP), 50 mg in 10 ml water as a nontoxic, nonabsorbable marker dye (9). Patients were randomly assigned to one of four groups: Group 1 (*n* = 35) received BSP, 50 mg + 150 ml water + placebo. Group 2 (*n* = 35) received BSP, 50 mg + 150 ml water + ranitidine, 150 mg. Group 3 (*n* = 35) received BSP, 50 mg + placebo. Group 4 (*n* = 35) received BSP, 50 mg + ranitidine, 150 mg.

General anesthesia was induced in all patients using intravenous thiopental, followed by nitrous oxide and oxygen supplemented with fentanyl. No other drugs were administered. At the end of surgery, which lasted an average of 10 min, an orogastric Salem sump-tube was passed and gastric contents aspirated with the patient in three different positions to facilitate maximal aspiration—lithotomy in the Trendelenburg position, horizontal supine, and left lateral positions. The pH of the aspirate was measured using a calibrated Radiometer PHM 82 pH meter and the BSP concentration using a Beckman spectrophotometer (9).

The percentage of ingested BSP remaining in the stomach was calculated by multiplying the measured concentration by the aspirated volume and expressing this as a percentage of the original 50 mg.

Results are given as mean \pm SD, and ranges where appropriate. Data were analyzed using one-way analysis of variance and Student's *t*-test. The χ^2 -analysis was used for comparisons between groups and to compare the proportions of patients in the four groups with pH less than 2.5, volume greater than 25 ml, or a combination of both risk factors. Correlation between patient characteristics and measured gastric volumes and acidity was sought using linear regression analysis. Differences were considered statistically significant when *P* was less than 0.05.

Results

There were no significant differences among the four groups with regard to age, weight, gestation, fasting interval, or the ingestion-surgery interval (Table 1). There was also no difference in the history of smoking, heartburn, or dyspepsia among the groups.

The volume, pH, and percentage BSP recovered in gastric contents are shown in Table 2. Patients who had 150 ml water with placebo (group 1) had significantly less residual gastric volume than did those

Table 3. Incidence of Patients in each Group with High Risk Factors^a

	Volume > 25 ml		pH < 2.5		Volume > 25 ml and pH < 2.5	
	Number	%	Number	%	Number	%
Group 1. (150 ml water + placebo)	8/35	23	31/31	100	8/35	23
Group 2. (150 ml water + ranitidine)	0/35	0	2/28	7	0/35	0
Group 3. (placebo)	18/35	51	16/33	48	16/35	46
Group 4. (ranitidine)	1/35	0	4/31	13	0/35	0

^aResidual gastric volume greater than 25 ml and pH less than 2.5

who had only BSP (group 3) whereas pH remained unchanged. Premedication with ranitidine (groups 2 and 4) significantly decreased both gastric volume and acidity compared with placebo (groups 1 and 3). Patients who drank 150 ml water with ranitidine (group 2) had significantly lower residual volumes and significantly higher pH levels than patients who had only BSP and placebo (group 3).

Virtually no BSP could be detected in the gastric fluid samples. The calculated percentage of dye remaining was extremely low in all patients, the maximum value being 0.09%, indicating that virtually all of the preoperative oral fluid had passed through the stomach by the time of surgery. No patient in group 1 had any dye detected in the gastric fluid, indicating complete gastric emptying of the oral fluid administered (Table 2).

The volume of gastric fluid in groups 1 and 2 (150 ml water) could not be correlated with the premedication interval, nor was there any correlation with duration of fast, patient's weight, smoking history, period of gestation, or history of heartburn or vomiting.

The incidence of patients with the combined high-risk factors of residual gastric volume greater than 25 ml and pH less than 2.5 is shown in Table 3. The drinking of 150 ml water significantly decreased this incidence, even in the placebo groups (group 2 vs 3). No patient premedicated with ranitidine (groups 2 and 4) fell into this high-risk category.

The severity of thirst on arrival in the operating room was significantly less than on admission in patients given 150 ml water (Fig. 1). Severity of hunger was unaltered.

Discussion

Pulmonary aspiration of gastric contents during anesthesia is a small but significant cause of anesthesia-related deaths, especially in obstetrics (10,11). Although precise numbers are not known, it is probable that many patients suffer nonfatal aspiration with significant morbidity. The severity of pulmonary damage

is related both to the volume and pH of the inhaled fluid, a combination of more than 25 ml with pH less than 2.5 being considered potentially lethal (12). Any safe treatment or management that reduces this hazard is desirable.

Several studies have demonstrated that the minimum fasting period of 5 hr in patients undergoing elective surgery does not predictably produce a safe gastric volume and pH (13,14). A more prolonged fast of up to 17 hr does not help, as more than one-third of patients still have the high-risk combination of a large gastric volume and low pH (5).

William Beaumont, in his studies on the fistulous stomach of Alexis St. Martin in 1825-1826, observed that fluids emptied rapidly in less than 1 hr (15). During the early years of anesthesia, patients were encouraged to take oral fluids, but not food, on the morning of surgery (16,17). In the 1920s, in Britain, clear fluids in the form of China tea, hot glucose water, or beef tea were given 3 hr before surgery (18,19). Since that time, the period of fasting for clear liquids as well as solids has been extended empirically so that it is now 5 or 6 hr (1,20) or simply nothing by mouth after midnight on the night before surgery (21).

The scientific basis for these changes is not clear. Both saline and glucose-water, unless very concentrated, empty rapidly (4). More than 90% of a 750-ml bolus of isotonic saline empties within 30 min in most patients (22). Furthermore, Miller et al. have shown that, in elective inpatients not receiving a narcotic premedication, tea and toast taken 2-4 hr preoperatively does not adversely affect the volume of gastric contents at the time of surgery (23). The opiates are potent antagonists of gastric emptying, and their role in elective premedication needs further evaluation in this context.

Ranitidine is a selective antagonist of histamine at gastric H₂ receptor sites. Maximum response to oral administration of the drug is achieved with a dose of 150 mg. It is rapidly absorbed after oral administration and inhibits both basal gastric secretions and gastric acid secretion induced by secretagogues. Peak plasma

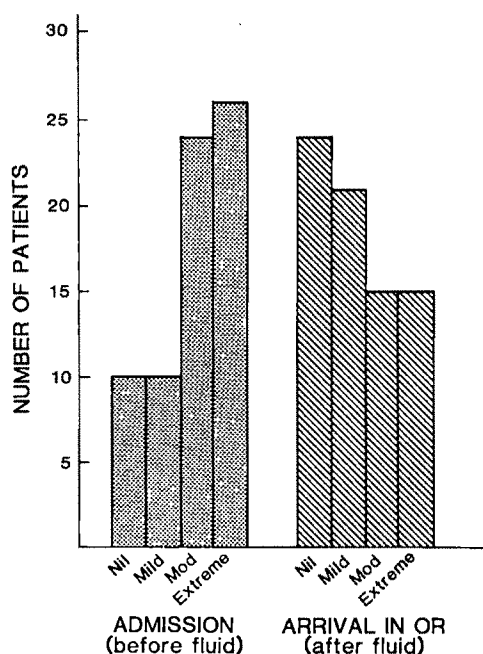


Figure 1. The effect of 150 ml water on the incidence and severity of thirst after 10 hr of fasting.

concentrations are achieved within 2–3 hr, and effective plasma concentrations persist for 8–12 hr (24).

The present study was undertaken to determine whether a 5-hr fast of fluids is necessary or even desirable. Because clear fluids are rapidly emptied from the stomach, it seemed possible that gastric volume and pH might be no worse after 150 ml water than after the traditional prolonged fast. Furthermore, because ranitidine reduces both the volume and acidity of gastric secretion, its use as premedication was expected to produce further improvement.

Our results support these hypotheses. In the patients studied, 150 ml water, even without ranitidine, significantly reduced gastric volume and pH. A possible explanation is that the ingested fluid increased the pressure gradient between the stomach and duodenum, stimulating gastric peristalsis and therefore gastric emptying (25). All our patients were ambulatory in the interval between receiving the dye and arrival in the operating room, so that it may be assumed that the dye was evenly mixed with stomach contents. The extremely low residual concentrations of dye remaining in the stomach at the time of surgery indicates that the gastric volume measured represents not just the fluid ingested with the dye but the gastric secretions produced after most of the dye had passed beyond the stomach. A further benefit of fluid administration found in this study was the significant reduction in preoperative thirst.

Gastric emptying is delayed in late pregnancy (26). However, in this study of first trimester patients, gastric emptying of fluid was rapid. The tone of the lower esophageal sphincter is known to be reduced, and the rate of emptying of the gallbladder decreases progressively during pregnancy (26,27). It is therefore possible that gastric hypomotility is also progressive during pregnancy, even though the volume and acidity of gastric secretions are not altered (14,26).

We conclude that the prolonged withholding of oral fluid does not improve the gastric volume and pH and may indeed worsen them. In this study, 150 ml water reduced residual gastric volume and increased patient comfort by decreasing thirst. Hunger was not altered. Gastric emptying of fluids is rapid in elective female outpatients, who remain ambulatory and who are not given narcotic premedication. It appears safe for such patients to drink up to 150 ml water, preferably with oral ranitidine 150 mg, 2–3 hr preoperatively.

The authors thank the daycare nursing staff and anesthesia colleagues for their cooperation; Mr. D.R. Kirk, gastrointestinal unit faculty technician, for laboratory analyses; and Mrs. C. Harris for secretarial assistance.

References

- Guidelines for the basic standards of practice of anaesthesia. The Canadian Anaesthetists' Society Inc, 1981:6.
- Mcrowitz M, Pounder DJ. Is the stomach a useful forensic clock? *Aust NZ J Med* 1985;15:273–6.
- Hinder RA, Kelly KA. Canine gastric emptying of solids and liquids. *Am J Physiol* 1977;233:E335–40.
- Hunt JN. Some properties of an alimentary osmoreceptor mechanism. *J Physiol* 1956;132:267–88.
- Stock GL, Sutherland AD. The role of H_2 receptor antagonist premedication in pregnant daycare patients. *Can Anaesth Soc J* 1985;32:463–7.
- Durrant JM, Strunin L. Comparative trial of the effect of ranitidine and cimetidine on gastric secretion in fasting patients at induction of anaesthesia. *Can Anaesth Soc J* 1982;29:446–50.
- McCrison DH, Dunn GL, Fargas-Babjak AM, Moudgil GC, Smedstad K, Woo J. A double-blind comparison of cimetidine and ranitidine as prophylaxis against gastric aspiration syndrome. *Anesth Analg* 1982;61:988–92.
- Davison JS, Davison MC, Hay DM. Gastric emptying in late pregnancy and labour. *J Obstet Gynaec Brit Comm* 1970;77:37–41.
- Shaffer EA, Small DM. Biliary lipid secretion in cholesterol gallstone disease. *J Clin Invest* 1977;59:828–40.
- Department of Health and Social Security. Report on confidential enquiries into maternal deaths in England and Wales 1976–78 London: Her Majesty's Stationery Office, 1982:96–100.
- Lunn JN, Mushin WW. Mortality associated with anaesthesia. London: Nuffield Provincial Hospital's Trust, 1982.
- Roberts RB, Shirley MA. Reducing the risk of gastric aspiration during cesarean section. *Anesth Analg* 1974;53:859–68.

13. Ong BY, Palahniuk RJ, Cumming M. Gastric volume and pH in outpatients. *Can Anaesth Soc J* 1978;25:36-9.
14. Sutherland T, Davies JM, Stock J. The price and value of pre-operative outpatient fasting—effects on gastric contents and outpatient morbidity. *Can Anaesth Soc J* 1985;32:S100.
15. Beaumont W. Gastric juice and the physiology of digestion. Plattsburgh: Allen, 1833:159-60, 277.
16. Lister J. On Anaesthetics, Part III. In: Holmes' System of Surgery, Vol III, 3rd ed. London, 1883. (Reprinted in: The Collected Papers of Joseph Lister. Birmingham: The Classics of Medicine Library, 1979:171-2.)
17. Snow J. On chloroform and other anaesthetics. London: Churchill, 1858:74-5.
18. Buxton DW. Anaesthetics: their uses and administration. London: Lewis, 1920:24-5.
19. Boyle HEG, Hewer CL. Practical anaesthetics, third edition. London: Frowde, Hodder and Stoughton, 1923:9.
20. Atkinson RS, Rushman GB, Lee JA. A Synopsis of Anaesthesia, 9th ed. Bristol: John Wright, 1982:96-7.
21. Orkin FK. Selection. In: Wetchler BV, ed. Anesthesia for Ambulatory Surgery. Philadelphia: Lippincott, 1985:106.
22. Goldstein H, Boyle JD. The saline load test—a bedside evaluation of gastric retention. *Gastroenterology* 1965;49:375-80.
23. Miller M, Wishart HY, Nimmo WS. Gastric contents at induction of anaesthesia. Is a four hour fast necessary? *Br J Anaesth* 1983;55:1185-8.
24. Douglas WW. Autocoids. In: Gilman AG, Goodman LS, Wall TW, Murad F, eds. Goodman and Gilman's the pharmacological basis of therapeutics, 7th ed. New York: Macmillan, 1985:624-7.
25. Carlson HC, Code CF, Nelson RA. Motor action of the canine gastroduodenal junction: a cineradiographic, pressure, and electric study. *Am J Dig Dis* 1966;11:155-72.
26. Van Thiel DH, Gavalier JS, Joshi SN, Sara RK, Stremple J. Heartburn of pregnancy. *Gastroenterology* 1977;72:666-8.
27. Braverman DZ, Johnson ML, Kern F Jr. Effects of pregnancy and contraceptive steroids on gallbladder function. *New Engl J Med* 1980;302:362-9.

Isoflurane Decreases the Cortisol Response to Cardiopulmonary Bypass

Paolo Flezzani, MD, Narda D. Croughwell, CRNA, R. William McIntyre, MD, and J. G. Reves, MD

FLEZZANI P, CROUGHWELL ND, MCINTYRE RW, REVES JG. Isoflurane decreases the cortisol response to cardiopulmonary bypass. *Anesth Analg* 1986;65:1117-22.

Eighteen patients with normal left ventricular function scheduled for elective myocardial revascularization were anesthetized with fentanyl (52-58 $\mu\text{g/kg}$). At the beginning of hypothermic cardiopulmonary bypass (CPB) they were assigned to a control (C) group ($n = 6$) that did not receive further anesthesia, or to a group given either 1% isoflurane ($n = 6$) or 2% isoflurane ($n = 6$). Blood samples for measurement of total plasma cortisol concentrations were obtained before, during, and after CPB. Hemodynamic mea-

surements before and after CPB were not different among groups. Patients in group C required higher infusion rates of sodium nitroprusside ($P \leq 0.05$) and patients given 2% isoflurane received more phenylephrine ($P \leq 0.05$) to keep mean arterial pressure at 50 ± 10 mm Hg during CPB. Isoflurane caused a dose-related decrease in total plasma cortisol concentrations during and after CPB. We conclude that increased depth of anesthesia attenuates the cortisol (stress) response to cardiopulmonary bypass.

Key Words: ANESTHESIA—cardiovascular. HORMONES—cortisol. ANESTHETICS, INTRAVENOUS—fentanyl. ANESTHETICS, VOLATILE—isoﬂurane.

Cardiopulmonary bypass (CPB) evokes a well-described stress response in patients with coronary artery disease, including increased plasma catecholamine levels (1) as well as cortisol levels (2). To test the hypothesis that the depth of anesthesia decreases the stress response to CPB we performed a dose-response study designed to measure the effect of isoflurane on cortisol blood levels during CPB.

Methods

After institutional approval, 18 adult patients scheduled to undergo elective coronary artery bypass grafting (CABG) gave informed consent and were entered into the study. All patients were premedicated with lorazepam, 0.04 mg/kg, and morphine sulfate, 0.1 mg/kg, 60-90 minutes before the scheduled time of operation. The administration of β -adrenergic and calcium-entry blocking medications was continued on the day of surgery. Venous, arterial, and thermodi-

lution pulmonary artery catheters were inserted percutaneously and 5-lead electrocardiographic monitoring was established before induction. General anesthesia was induced with fentanyl (30 $\mu\text{g/kg}$) and muscle relaxation was achieved with pancuronium bromide (0.15 mg/kg). Anesthesia was maintained with a continuous infusion of fentanyl at a rate of 0.2 $\mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$, and the patient was ventilated with 100% oxygen. The fentanyl infusion was stopped 5 min before institution of CPB, at which point the patients were randomly assigned to a control group (C) that received no further anesthetic or to groups that received either 1% or 2% inspired concentrations of isoflurane through a calibrated vaporizer in line with the oxygen circuit of the extracorporeal circulation system. The administration of isoflurane was terminated 5 min after the release of the aortic cross-clamp. Fresh gas flow was kept above 4 L/min. Cardiopulmonary bypass was performed using either bubble or membrane oxygenators with prime volumes of 1500-2200 ml lactated Ringer's solution and 200 ml 25% albumin. The pump flow was maintained at 1.6-2.0 $\text{L}\cdot\text{min}^{-1}\cdot\text{m}^{-2}$; it was not altered to change perfusion pressure. Sodium nitroprusside and phenylephrine infusions were used to maintain a mean arterial pressure at 50 ± 10 mm Hg. Sampling of arterial blood for measurements of total plasma cortisol and hemo-

Presented in part at the 8th Annual Meeting of the Society of Cardiovascular Anesthesiologists, April, 1986. Supported by a grant from Anaquest, Inc.

Received from the Division of Cardiothoracic Anesthesiology, Department of Anesthesiology, Duke University Medical Center, Durham, North Carolina. Accepted for publication June 17, 1986.

Address correspondence to Dr. Flezzani, Assistant Professor of Anesthesiology, Box 3071 DUMC, Durham, NC 27710.

Table 1. Demographic Data

	Control	1% Isoflurane	2% Isoflurane
Age (yr)	58 ± 2	58 ± 4	53 ± 3
Weight (kg)	77.8 ± 4.2	87.5 ± 5.2	84.2 ± 4.3
BSA (kg/m ²)	1.9 ± 0.05	2.0 ± 0.08	2 ± 0.08
LVEDP (mm Hg)	11 ± 2	14 ± 2	14 ± 2
EF (%)	0.53 ± 0.04	0.58 ± 0.01	0.52 ± 0.04
CI (l·min ⁻¹ ·m ⁻²)	2.9 ± 0.2	2.2 ± 0.4	2.7 ± 0.3

All values are mean ± SEM.

Abbreviations: BSA, body surface area; LVEDP, left ventricular end diastolic pressure; EF, ejection fraction; CI, cardiac index.

dynamic observations were made at the following times:

- A) 15 min after tracheal intubation
- B) Immediately after initiation of CPB
- C) 30 min after cross-clamping of the aorta
- D) 2 min after release of the aortic cross-clamp
- E) 10 min after release of the aortic cross-clamp
- F) Immediately after termination of CPB
- G) Immediately after infusion of protamine sulfate
- H) Immediately after closure of the sternum.

Total plasma cortisol levels in whole blood samples were determined by radioimmunoassay technique (3). Derived hemodynamic variables were calculated from standard formulas.

Between-group statistical analysis was performed by one-way analysis of variance and within group analysis was performed by a repeated measures analysis of variance. A *P* value ≤0.05 was considered statistically significant. Pair-wise comparisons between group means was done with the Fisher's protected least significant difference test.

Results

Demographic data, preoperative hemodynamic data, and medical management were similar in the groups (Table 1). Total plasma cortisol concentrations, not corrected for hemodilution, are shown in Figure 1. Isoflurane had a dose-related effect on cortisol levels: the higher the dose the lower the cortisol plasma levels. Two percent isoflurane, for example, was associated with plasma cortisol levels that were significantly lower than in control patients. This effect started at 30 min on CPB, continued after the administration of isoflurane was terminated and was still present at the conclusion of the procedure. Plasma cortisol levels associated with 1% isoflurane were intermediate between the control group and the 2% group. There was no difference between groups with regard to the

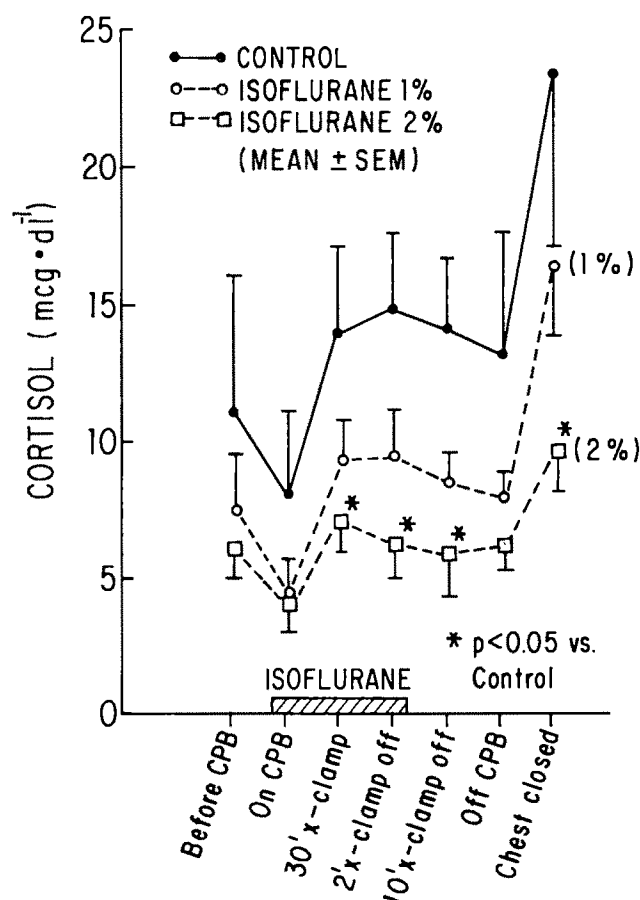


Figure 1. Plasma cortisol levels ($\mu\text{g}/\text{dl}$) measured at different times during CABG. CPB, cardiopulmonary bypass; x-clamp, aortic cross-clamp.

amount of fentanyl given, duration of CPB, duration of aortic cross clamp (Table 2), total amount of fluids added during CPB, and total amount of cardioplegia used (Table 3). Directly measured and derived hemodynamics were not different during and after CPB (Table 4). During CPB, the maximal infusion rate of sodium nitroprusside was significantly greater in the control group and the 2% isoflurane group received more phenylephrine (Fig. 2). There was no recall of surgery, mortality, documented perioperative myocardial infarction, or need for inotropic support in any group.

Discussion

The effects of CPB on cortisol plasma levels are controversial. Taylor et al. (4) observed that concentrations of total plasma cortisol, as measured by fluorometry, decreased after the onset of CPB, and then increased gradually after CPB, reaching a peak 24 hr

Table 2. Fentanyl Dose and Duration of Cardiopulmonary Bypass

	Control	1% Isoflurane	2% Isoflurane
Fentanyl ($\mu\text{g/kg}$)	52 ± 3	56 ± 5	56 ± 3
CPB (min)	154 ± 18	158 ± 25	133 ± 9
Cross-clamp time (min)	74 ± 12	63 ± 8	59 ± 9

All values are mean \pm SEM.

after CPB. However, when cortisol values were corrected for hemodilution, total plasma cortisol levels during CPB were comparable to those before CPB. When synthetic ACTH was administered to these patients, total plasma cortisol levels increased, reflecting normal adrenal function. In another study, biologically active free cortisol remained at pre-CPB levels during CPB, probably because of changes in protein binding properties (5). In contrast to those findings, Oka et al. found that total plasma cortisol increased both during and after CPB in patients undergoing coronary artery bypass procedures (6). They concluded that cortisol levels increased with catecholamine levels and that this represented a generalized stress response to CPB.

There is a considerable body of research concerning the effect of anesthetics, primarily narcotics, on the cortisol response during surgery in cardiac surgical patients. However, the majority of this research is confined to the period prior to CPB. Morphine, 2-4 mg/kg intravenously, blunted or suppressed the cortisol response to initial surgical stimulation (7-9) but, during CPB, total plasma cortisol increased in spite of high-dose morphine anesthesia (4 mg/kg). Synthetic narcotics have been investigated in this context with conflicting results for the CPB period, probably because of different dose regimens (10-13). However, in general, narcotics appear to be ineffectual in blocking increase in plasma cortisol levels during CPB. There is a paucity of data on the effects of inhalational agents on cortisol levels during CPB. The effects of halothane (14-17), isoflurane (18,19), and enflurane (20) on plasma levels of cortisol during noncardiac surgery and before CPB for cardiac surgery have been investigated. The results of these studies demonstrated variable effects of inhalational agents, from no change to a twofold increase in cortisol, depending on the study design. High-dose fentanyl appears to be more effective than low-dose inhalational anesthesia (0.5-1%), with or without nitrous oxide. None of these studies compared equipotent doses of agents or investigated anesthetic dose-responses during CPB.

The results of our study demonstrate that total plasma cortisol levels decrease below pre-CPB levels

Table 3. Total Fluid Volume Addition during Cardiopulmonary Bypass

	Control	1% Isoflurane	2% Isoflurane
Volume added during CPB (ml)	1200 ± 386	1880 ± 700	1600 ± 226
Cardioplegia (ml)	1292 ± 132	1158 ± 71	1017 ± 145

with initiation of CPB, and then increase during CPB. These results confirm the findings of Oka et al. (6). In most other studies, the sampling schedule during CPB yielded limited information. The initial decrease in cortisol levels probably reflects hemodilution and the subsequent increase represents increased release and/or decreased metabolism during CPB.

Several questions are raised by our results. First, could the different results between control and isoflurane groups be due to a light level of anesthesia in the control group? We did not measure fentanyl plasma concentrations. However, a fentanyl dose of 50-60 $\mu\text{g/kg}$ blunts the pre-CPB cortisol response to surgery and is claimed to have the same effect during CPB (9-11). A higher fentanyl dose or continuous infusion during CPB might possibly have attenuated the cortisol response to CPB seen in group C. Samuelson et al. showed that an additional injection of sufentanil just before CPB was associated with lower catecholamine levels than unsupplemented sufentanil (10 $\mu\text{g/kg}$) (21). Second, is the effect of isoflurane specific or is it related to deeper anesthesia? Our study does not address this question. The data of Samuelson et al. suggest that any anesthetic can suppress the stress response, if given in sufficient amounts (21). However, in their study, they also showed that an inhalational anesthetic (enflurane) is more effective than a narcotic (sufentanil) in decreasing the catecholamine response to CPB. It is not known whether equipotent doses of enflurane and sufentanil were used. Finally, what is the effect of hypothermia and hemodilution on the uptake and distribution of isoflurane during CPB? It is well known that the blood gas partition coefficient of inhalational anesthetics increases with decreasing temperature, an effect opposed by hemodilution (22). The net effect on the blood gas solubility coefficient is a slight decrease, resulting in a higher concentration of isoflurane in the tissue. Whether this effect has clinical importance is not known.

In conclusion, isoflurane, in a dose-related fashion, blunted the increase in plasma levels of cortisol during CPB cortisol release, supporting our hypothesis that depth of anesthesia affects cortisol response to the

Table 4. Hemodynamics

	A	B	C	D	E	F	G	H
Control								
HR (beats/min)	63 ± 5	56 ± 7	—	—	38 ± 13	85 ± 4	81 ± 2	91 ± 4
MAP (mm Hg)	83 ± 3	48 ± 4	52 ± 5	51 ± 4	54 ± 5	75 ± 4	80 ± 1.5	81 ± 3
CI (l·min ⁻¹ ·m ⁻²)	2.3 ± 0.3	2.5 ± 0.07	1.6 ± 0.1	2.4 ± 0.1	2.7 ± 0.2	3.0 ± 0.1	2.6 ± 0.09	2.3 ± 0.2
PCWP (mm Hg)	9 ± 1	—	—	—	—	8.8 ± 0.9	8.6 ± 1.8	10 ± 2
SVR (dynes·cm ⁻⁵)	1468 ± 209	732 ± 63	1481 ± 257	935 ± 79	789 ± 196	932 ± 94	1148 ± 32	1355 ± 117
LVSWI (gm·m ⁻²)	38 ± 3	—	—	—	—	32 ± 3	32 ± 2	24 ± 3
RPP (beats·mm Hg·min ⁻¹) × 10 ³	7.6 ± 0.5	—	—	—	—	9.4 ± 0.7	9.4 ± 0.7	10.2 ± 0.6
1% Isoflurane								
HR (beats/min)	68 ± 8	70 ± 11	—	—	40 ± 20	89 ± 4	94 ± 2	96 ± 1
MAP (mm Hg)	92 ± 2	55 ± 3	49 ± 4	53 ± 4	63 ± 5	71 ± 4	80 ± 39	87 ± 3
CI (l·min ⁻¹ ·m ⁻²)	2.1 ± 0.3	2.3 ± 0.04	1.6 ± 0.2	2.3 ± 0.1	2.5 ± 0.2	2.9 ± 0.3	2.4 ± 0.6	1.9 ± 0.2
PCWP (mm Hg)	10 ± 2	—	—	—	—	10 ± 0.7	8 ± 5	10 ± 1
SVR (dynes·cm ⁻⁵)	1780 ± 243	875 ± 87	1167 ± 110	810 ± 57	1036 ± 117	909 ± 139	2613 ± 1526	1636 ± 156
LVSWI	34 ± 2	—	—	—	—	27 ± 3	26 ± 7	23 ± 2
RPP (beats·mm Hg·min ⁻¹) × 10 ³	9.2 ± 1.2	—	—	—	—	8.8 ± 0.5	102 ± 0.6	11.2 ± 0.3
2% Isoflurane								
HR (beats/min)	69 ± 5	65 ± 3	—	12 ± 8	56 ± 2	84 ± 4	85 ± 7	87 ± 3
MAP (mm Hg)	94 ± 7	45 ± 5	48 ± 4	48 ± 4	57 ± 5	72 ± 6	68 ± 7 ^{a,b}	75 ± 8
CI (l·min ⁻¹ ·m ⁻²)	2.2 ± 0.2	2.4 ± 0.08	2 ± 0.2	2.4 ± 0.1	2.6 ± 0.08	2.6 ± 0.2	2.3 ± 0.2	2.6 ± 0.3 ^b
PCWP (mm Hg)	7 ± 0.8	—	—	—	—	11 ± 2	9 ± 2	9 ± 0.9
SVR (dynes·cm ⁻⁵)	1714 ± 209	743 ± 105	993 ± 94	778 ± 85	895 ± 107	1028 ± 130	1096 ± 21	1089 ± 138 ^b
LVSWI	39 ± 5	—	—	—	—	26 ± 3	28 ± 2	30 ± 6
RPP (beats·mm Hg·min ⁻¹) × 10 ³	9.4 ± 1.1	—	—	—	—	8.9 ± 0.7	8.3 ± 0.7	9.6 ± 0.7

All values are mean ± SEM.

Abbreviations: A, 15 min after intubation; B, immediately after initiation of CPB; C, 30 min after cross-clamping of the aorta; D, 2 min after release of the aortic cross-clamp; E, 10 min after release of the aortic cross-clamp; F, immediately after the termination of CPB; G, immediately after infusion of protamine sulfate; H, immediately after closure of the sternum; HR, heart rate; MAP, mean arterial pressure; CI, cardiac index; PCWP, pulmonary capillary wedge pressure; SVR, systemic vascular resistance; RPP, rate pressure product; LVSWI, left ventricular stroke work index.

^aDifference from control, $P \leq 0.05$.^bDifference from 1% isoflurane, $P \leq 0.05$.

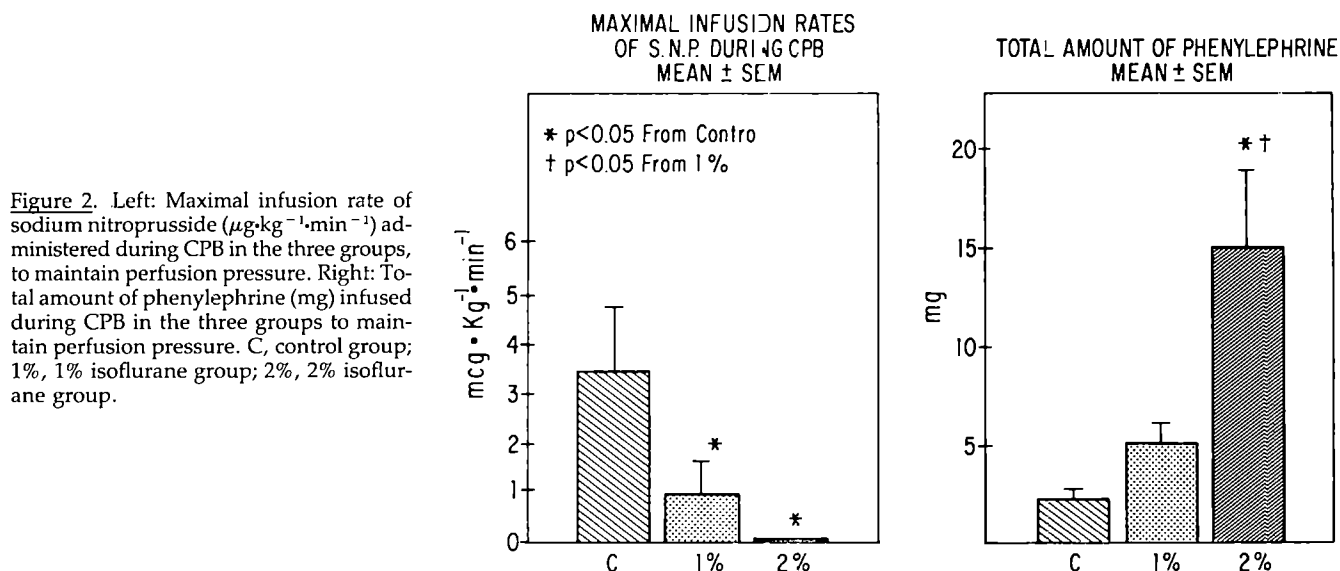


Figure 2. Left: Maximal infusion rate of sodium nitroprusside ($\mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$) administered during CPB in the three groups, to maintain perfusion pressure. Right: Total amount of phenylephrine (mg) infused during CPB in the three groups to maintain perfusion pressure. C, control group; 1%, 1% isoflurane group; 2%, 2% isoflurane group.

stress of CPB. In addition to these findings during CPB, our data demonstrate an effect of isoflurane that persists into the period after CPB, at a time when the effects of isoflurane would be expected to be waning. This effect suggests that the mechanism affecting plasma cortisol levels after the end of bypass is related to the stress of CPB rather than to surgery per se, and could mean also that the clearance of cortisol might be prolonged after CPB. Further investigation is needed to determine whether this persistence is specific for isoflurane or a common property of all anesthetic agents. It is also important to ascertain whether stress suppression during CPB can favorably affect organ function after CPB.

The authors acknowledge the assistance of Dr. Warner Burch, Director of Endocrinology Laboratory, Duke University Medical Center, for measurements of cortisol levels.

References

- Reves JG, Karp RB, Buttner EE, Jacon ES, Smith LR, Samuelson PN, Kreusch GR, Oparil S. Neuronal and adrenomedullary catecholamine release in response to cardiopulmonary bypass in man. *Circulation* 1982;66:48-55.
- Frater RWM, Wakagama S, Oka Y. Pulsatile cardiopulmonary bypass: failure to influence hemodynamics or hormones. *J Thorac Cardiovasc Surg* 1981;81:396-9.
- Ruder HJ, Guy RL, Lipsett MB. A radioimmunoassay for cortisol in plasma and urine. *J Clin Endocrinol Metab* 1972;35:219-24.
- Taylor KM, Jones JV, Walker MS, Rao S, Bain WH. The cortisol response during heart-lung bypass. *Circ* 1976;54:20-5.
- Taylor KM, Bain WM, Jones JV, Walker MS. The effect of hemodilution on plasma levels of cortisol and free cortisol. *J Thorac Cardiovasc Surg* 1976;72:57-61.
- Oka Y, Wakajama S, Oyama T, et al. Cortisol and antidiuretic hormone responses to stress in cardiac surgical patients. *Can Anaesth Soc J* 1981;28:334-337.
- Brandt MR, Korshin J, Hansen P, et al. Influence of morphine anaesthesia on the endocrine-metabolic response to open-heart surgery. *Acta Anaesthesiol Scand* 1978;22:400-12.
- George JM, Reier CE, Lanese RR, Rower JM. Morphine anesthesia blocks cortisol and growth hormone response to surgical stress in humans. *J Clin Endocrinol Metab* 1974;38:736-41.
- Reier CE, George JM, Kilman JW. Cortisol and growth hormone response to surgical stress during morphine anesthesia. *Anesth Analg* 1973;52:1003-10.
- Walsh ES, Paterson JL, O'Riordan RBA, Hall GM. Effect of high dose fentanyl anaesthesia on the metabolic and endocrine response to cardiac surgery. *Br J Anaesth* 1981;53:115E-65.
- Seibel PS, Bovill JG, Schellekens APM, Harker CD. Hormonal response to high dose fentanyl anaesthesia. *Br J Anaesth* 1981;53:941-7.
- de Lange S, Stanley TH, Boscoe MJ, et al. Catecholamine and cortisol responses to sufentanil- O_2 and alfentanil- O_2 anaesthesia during coronary artery surgery. *Can Anaesth Soc J* 1983;30:248-54.
- Stanley TH, Berman L, Greene D, Robertson D. Plasma catecholamines and cortisol response to fentanyl-oxygen anaesthesia for coronary-artery operations. *Anesthesiology* 1980;53:250-3.
- Sojanos E, Alevizou F, Zissis N, Kostaki P, Balamoutsos N. Hormonal response in thoracic surgery: effects of high dose fentanyl anaesthesia, compared to halothane anaesthesia. *Acta Anaesthesiol Belg* 1985;36:89-96.
- Campbell BC, Parikh RK, Naismith A, Sewnauth D, Reid JL. Comparison of fentanyl and halothane supplementation to general anaesthesia on the stress response to upper abdominal surgery. *Br J Anaesth* 1984;56:257-61.
- Kono K, Philbin DM, Coggins CM, et al. Renal function and stress response during halothane or fentanyl anaesthesia. *Anesth Analg* 1981;60:552-6.
- Hall GM, Young C, Holdcroft A, Alaghband-Zadeh J. Substrate mobilisation during surgery. A comparison between halothane and fentanyl anaesthesia. *Anaesthesiol* 1978;33:924-30.
- Geman S, Rivas JE, Erdemir H, et al. Hormonal and haemodynamic responses to upper abdominal surgery during isoflurane and balanced anaesthesia. *Can Anaesth Soc J* 1984;31:509-16.

19. Oyama J, Latta P, Holaday DA. Effect of isoflurane anaesthesia and surgery on carbohydrate metabolism and plasma cortisol levels in man. *Can Anaesth Soc J* 1975;92:696-702.
20. Abdulla YW, Giesecke AM, Tillman Hein HA, Cordes U. A comparison of the activity of the sympathoadrenal and adrenocortical system under inhalation anaesthesia techniques. *Acta Anaesthesiol Belg* 1983;34:257-64.
21. Samuelson PN, Reves JG, Kirklin JK, Bradley E, Wilson KD, Adams M. Sufentanil versus enflurane nitrous oxide anesthesia for myocardial revascularization—a prospective randomized comparison. *Anesth Analg* 1986;65:217-26.
22. Feingold A. Crystalloid hemodilution, hypothermia, and halothane blood solubility during cardiopulmonary bypass. *Anesth Analg* 1977;56:622-76.

Effects of Ketamine on Low Intensity Tactile Sensory Input Are Not Dependent upon a Spinal Site of Action

J. G. Collins, PhD

COLLINS JG. Effects of ketamine on low intensity tactile sensory input are not dependent upon a spinal site of action. *Anesth Analg* 1986;65:1123-9.

The development of a technique for studying spinal dorsal horn electrophysiology in intact, awake, drug-free cats enables the study of spinal sites and mechanisms of action of anesthetic and analgesic agents in a system that more closely reflects normal physiology. Using this technique, we re-evaluated the effect of ketamine on spinal dorsal horn sensory transmission. The results of our study confirm previous work done in acute preparations. Ketamine (maximum dose 20 mg/kg) did not significantly reduce the response of low threshold ($n = 11$) dorsal horn neurons to low intensity

sensory stimulation. However, that same dose of ketamine did suppress noxious evoked activity of the two wide dynamic range neurons encountered in the study, while having a varied effect on neurons responsive to proprioceptive input ($n = 7$). These findings confirm that, in the intact animal with all modulatory systems intact, ketamine "dissociation" of low intensity tactile stimuli does not appear to involve a spinal mechanism of action. The results also support the importance of spinal sites of action for the analgesia produced by ketamine, as well as the importance of distinguishing between the anesthetic and analgesic effects of that drug.

Key Words: ANESTHETICS, INTRAVENOUS—ketamine. SPINAL CORD—ketamine.

A knowledge of the sites within the nervous system (peripheral and/or central) at which an anesthetic is capable of blocking sensory transmission would help to better define the means by which anesthesia is produced. The unique behavioral effects of ketamine have prompted investigators to study its sites and mechanisms of action. Two key studies in the early 1970s presented evidence that part of the anesthetic/analgesic effect of ketamine was due to a spinal mechanism of action (1,2). Those studies suggested that the analgesic effect of ketamine may be dependent upon a spinal action, whereas initial clinical reports (3) suggested that the dissociative anesthesia produced by the drug may be due to supraspinal disruption of somesthetic information. An important difference between previous studies of the spinal effects of ketamine and this present study is the animal preparation. This study is the first report on the effect of ketamine on dorsal horn neurons in physiologically intact, awake, drug-free animals (chronic preparation). All previous studies were conducted in animals that were anesthetized and/or decerebrate and/or had

their spinal cords transected (acute preparations). Thus, previous acute studies involved procedures that may have altered systems through which ketamine produces its effect in an intact animal (e.g., descending inhibitory systems that may modulate spinal dorsal horn neuronal activity). The purpose of this study was to examine, in intact animals, the effects of systemically administered ketamine on the response properties of spinal dorsal horn neurons.

Methods

Institutional, state, and federal guidelines for the humane care and use of laboratory animals were followed during all phases of this study. Electrical activity of single spinal dorsal horn neurons was recorded extracellularly from physiologically intact, awake, drug-free cats. A detailed description of the recording technique has been reported previously (4). Animals were trained to sit quietly in a restraint box. Under general anesthesia and using sterile technique, a recording chamber was surgically attached to the animal's vertebral columns over a 6×12 mm opening in the bone (dura mater remains intact) that was made over the lumbar enlargement. The chamber provided a window to the bone opening through which recording microelectrodes could be positioned in the dorsal horn of the spinal cord. A chronic external jugular vein

Supported by NIH Grant GM29065.

Received from the Department of Anesthesiology and Pharmacology, Yale University School of Medicine, New Haven, Connecticut. Accepted for publication May 15, 1986.

Address correspondence to Dr. Collins, Department of Anesthesiology and Pharmacology, Yale University School of Medicine, 333 Cedar Street, New Haven, CT 06510.

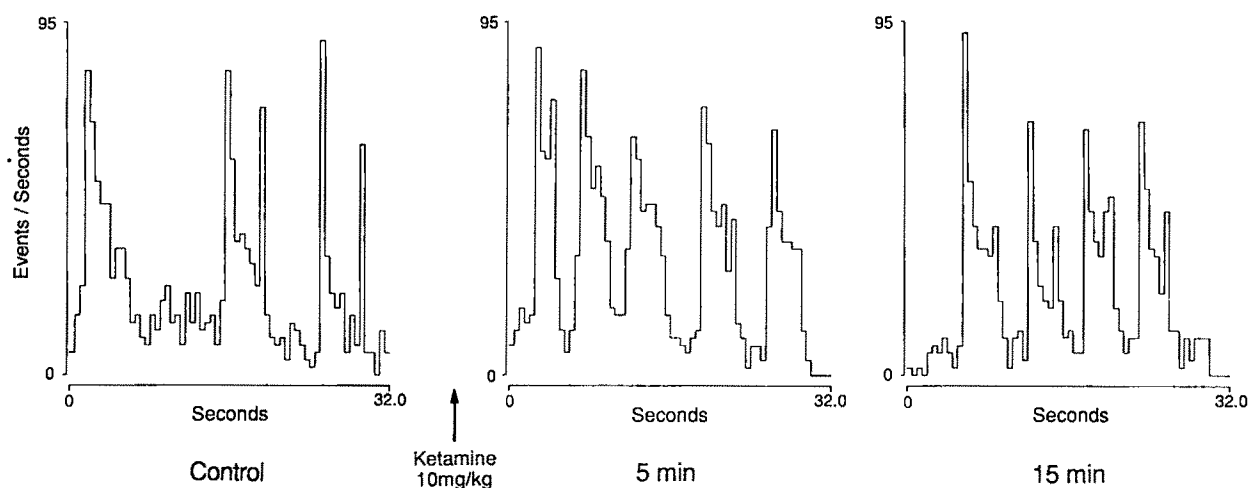


Figure 1. Response of an LT neuron to receptive field stimulation by a calibrated von Frey monofilament (von Frey monofilaments deflect at a constant pressure, and thus provide a means of presenting a repeatedly quantifiable stimulus to a cell's receptive field). The y axis represents the number of action potentials expressed as events per second. Initial contact with the receptive field caused a high burst of activity as indicated by an initial high peak. Thus, each stimulus presentation is associated with either an initial high peak rate of activity with a decreasing response or an initial high peak followed by a secondary peak a few seconds later. During control studies, the receptive field was stimulated three times by the filament. This cell adapted rapidly to the stimulus, but responded again when the filament was removed from the skin, as demonstrated by the second and third stimulus presentations during control where a large spike is produced at the instant that the monofilament was removed from the skin. Five minutes after 10 mg/kg of ketamine, the mean response of this neuron to stimulus presentation was 116% of control; 15 min after ketamine administration, the response was still 96% of control.

catheter was implanted and externalized on the head. A minimum of 2 weeks separated the surgical implantation of catheter and chamber from the start of electrophysiological studies.

For each experiment, an electrode was inserted into the spinal cord and removed at the end of the experiment. Dural penetration produced no obvious discomfort to the animal. The electrode was advanced in micron steps while the skin of the animal was stimulated (hindlimbs and hips). When the height of the recorded signal from one cell was sufficiently greater than the height of all other recorded signals (amplitude discrimination), the response properties of that neuron to various stimuli were evaluated. This separation by amplitude of the action potential of the cell of interest from all other recorded signals was maintained for the duration of each cell's study. If the separation in height decreased such that we were not convinced that activity was being recorded from only one cell, the data were not included in the analysis. The receptive field of the neuron was mapped on the

surface of the skin, and the field was then stimulated by air puff, von Frey filaments, brushing, rubbing, squeezing, pinching, heating, and cooling. Cooling was produced by a 2-sec spray of ethyl chloride on the skin (evaporative cooling). Pinch and heat were used as noxious stimuli. Pinch was produced either with forceps or with the experimenter's fingers, and was increased in intensity until a reflex withdrawal was elicited. Heating was achieved by focusing a radiant heat source on the receptive field. Skin temperature (monitored by a thermocouple on the skin surface) was increased until a reflex response was elicited (typically 44–46°C). In addition to the above stimuli, joint rotation and deep pressure on muscle were used to test a neuron's response to proprioceptive input. Spontaneous activity, if present, was also recorded.

Quantification of the radiant heat stimuli was assured by skin temperature monitoring. Quantification of nonnoxious mechanical stimuli was less precise. The use of calibrated von Frey filaments, as shown in Figure 1, made it possible to present repeatedly the same punctate mechanical stimulus. Although variable from stimulus to stimulus, air puff, rubbing, and heating can, by repeated, careful presentations, produce an average response that can be compared before and after drug administration. In the control situation, several series of these stimuli can be administered to produce neuronal activity that is very similar with regard to the overall activity that the stimuli elicit.

After isolation and characterization of the neuron, as described above, the effects of ketamine were tested. An initial dose of 10 mg/kg of ketamine was administered intravenously, and spontaneous and stimulus-evoked activity were recorded for a period of up to 10 min. In several experiments, an additional dose of

10 mg/kg of ketamine was administered. Activity was recorded for an additional 10 min, resulting in a cumulative dose of 20 mg/kg observed over a 20 min time period.

Spontaneous firing rates were determined by averaging the activity over two 30 sec periods during control studies and subsequent to drug administration. Evoked firing rates were determined by averaging the response to repetitive stimuli during the control period and after drug administration. Statistical analysis of the data, as recommended by several statisticians, was most appropriately carried out by Student's *t*-test. To avoid the problems associated with repeated uses of Student's *t*-test in analyzing the same data, *P* values of 0.01, rather than 0.05, were accepted as significant, and, in addition, no more than three tests were performed on any group of data.

In representative experiments, electrolytic lesions were made through the recording electrode at the end of an experiment. In this study four of the animals each received three lesions. None of the cells reported in this study was located on the same side of the cord as the lesions. When animals were judged to be unlikely to yield additional data (typically 1-2 months after implantation), they were killed by barbiturate overdose. Spinal cord sections were fixed and prepared histologically for examination of recording sites.

Results

Data for this study were obtained from seven animals. To maximize the amount of information obtained, each animal was used for several different types of studies during the time that it was available for recording. Experimental protocols were alternated so that animals typically were not used for the same type of experiment on subsequent days. The only other drug studied in these animals, during the time that they were being utilized for this ketamine study, was naloxone at a maximum dose of 0.4 mg/kg. All animals were drug-free for a minimum of 24 hr before their use in the ketamine study. Typically, data were not recorded from any animal more than twice a week. A total of 30 neurons was recorded during the ketamine study. Intravenous ketamine administration caused some animals to experience an excitatory phase that, although very brief in duration, was intense enough to cause the loss of several neurons. Data presented in this study, therefore, were obtained from 11 low threshold (LT), two wide dynamic range (WDR), and seven proprioceptive neurons. The apparent underrepresentation of WDR neurons will be discussed. Representative lesions indicated that recording sites centered on Rexed laminae IV-VI.

Table 1. Effect of Ketamine (10 mg/kg) on LT Neuronal Evoked Activity

Control	5 min ^a	10 min ^a
100%	115.6 ± 12.1% (<i>n</i> = 11)	101.4 ± 7.3% (<i>n</i> = 8)

^aValues are mean percent of control ± SEM.

Within 1 min of drug administration, all animals were unresponsive to external stimuli and demonstrated the behavior typically associated with dissociative anesthesia.

Low Threshold Neurons

The low threshold (LT) neurons (*n* = 11) were similar, in many ways, to LT neurons recorded from the spinal dorsal horn in acute experiments (5). Both their response properties and receptive field sizes were comparable to those reported in acute animals. The most obvious difference between the low threshold neurons in this study and those reported previously in acute studies was the lack of spontaneous activity in the intact animal. Eight of the 11 LT neurons had control spontaneous firing rates of less than one impulse per second. The remaining three had rates of 3.2, 2.7, and 1.9 impulses per second. Four of the LT neurons demonstrated absolutely no spontaneous activity whatsoever in the absence of stimulus presentation. In spite of the absence of spontaneous activity, the neurons responded well to low intensity stimulation and responses did not increase with increasing intensity of stimulus presentation. Thus, the response profile allowed them to be classified as low threshold neurons. Table 1 demonstrates that the administration of 10 mg/kg of ketamine did not cause a reduction in the mean firing rate of all the LT neurons studied. Activity of any one cell showed very little variability during control conditions. Although the mean of the stimulus-evoked activity of the LT neurons studied was not reduced by ketamine, there was, as indicated by the standard errors, some individual variability. At both 5 and 10 min after ketamine administration, one neuron had its evoked activity reduced to approximately 75% of the control value. At 5 min, four LT neurons demonstrated a significant increase in their stimulus-evoked activity. At 10 min, two of those neurons were still excited by ketamine. Three of the LT neurons were studied after an additional 10 mg/kg of ketamine administered 10 min after the initial dosing. The additional dose of ketamine produced no significant change in the evoked activity of any of those neurons. The lack of significant suppression of LT

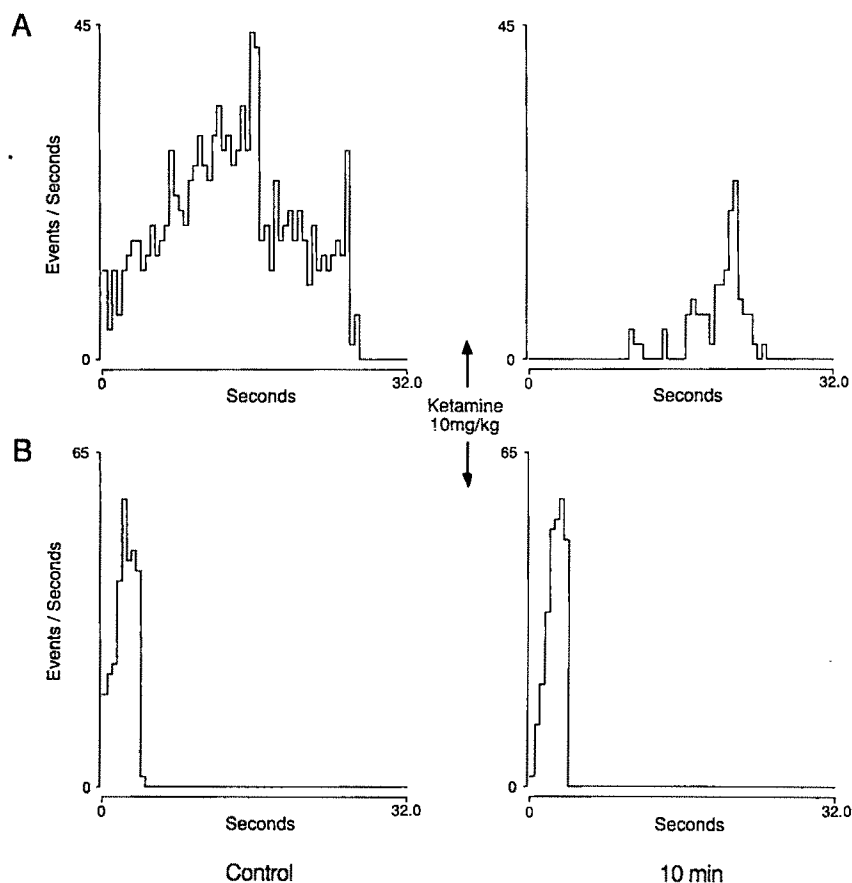


Figure 2. Ketamine effect (10 mg/kg), on noxiously evoked (A) and low intensity evoked (B) activity of a WDR neuron. The y axis represents the number of action potentials expressed as events per second. In A, the thermal stimulus was turned on at time zero and off 15 sec later. In B, brushing the receptive field began at time zero and ended with the end of activity approximately 4 sec later. The response of this WDR neuron to skin heating (46°C maximum) was suppressed to 26% of control 10 min after ketamine administration. In contrast, the activity evoked in the same neuron by light brushing of the skin was maintained at 96% of control 10 min after ketamine administration. These results demonstrate a clear separation between the ability of ketamine to affect noxious and nonnoxious somesthetic information in the lumbar dorsal horn of the spinal cord.

evoked activity is shown in Figure 1 for a single LT neuron that was activated by the presentation of a calibrated von Frey filament to the cell's receptive field.

Wide Dynamic Range Neurons

The initial intent of this study was to evaluate a large number of wide dynamic range WDR neurons. Our studies to date in intact animals suggest that neurons with a WDR response profile (increased firing rate with increased stimulus intensity until maximum rate is achieved with noxious stimulus) may be less common in the lumbar enlargement of intact animals than in acute preparations. Of the total neurons encountered in this study, only two were classified as having a wide dynamic range response profile during control studies. Both WDR neurons had their noxious radiant heat-evoked activity significantly reduced by the 10 mg/kg dose of ketamine. This reduction in activity occurred in spite of the fact that the temperature and duration of the stimulus was the same as that used during control studies. The reduction was to 26 and 7% of control at 10 min. Figure 2 demonstrates that, although the noxiously evoked activity of a WDR neu-

ron was greatly suppressed by ketamine, the response of that same neuron to nonnoxious, low intensity, tactile stimulation was not significantly altered by the same dose at the same time.

Proprioceptive Neurons

The final group of neurons ($n = 7$) studied was found to be affected in various ways by ketamine. All of these neurons were classified as proprioceptive in nature based on their exclusive response to either joint rotation or deep pressure on muscle. All of these neurons fired spontaneously in the absence of experimenter-induced stimulation. However, this activity was probably not truly spontaneous because normal muscle tone and joint position in the intact animal is likely to be a source of stimulation for proprioceptive neurons. Ten minutes after 10 mg/kg of ketamine, two of the proprioceptive neurons had reduced firing rates to levels of 20 and 65% of control. Four of the cells had rates that were increased (127, 418, 529, and 271% of control), and one cell was relatively unaffected by ketamine (90% of control). In one of these experiments, an additional 10 mg/kg of ketamine was administered 10 min after the initial dosing and was

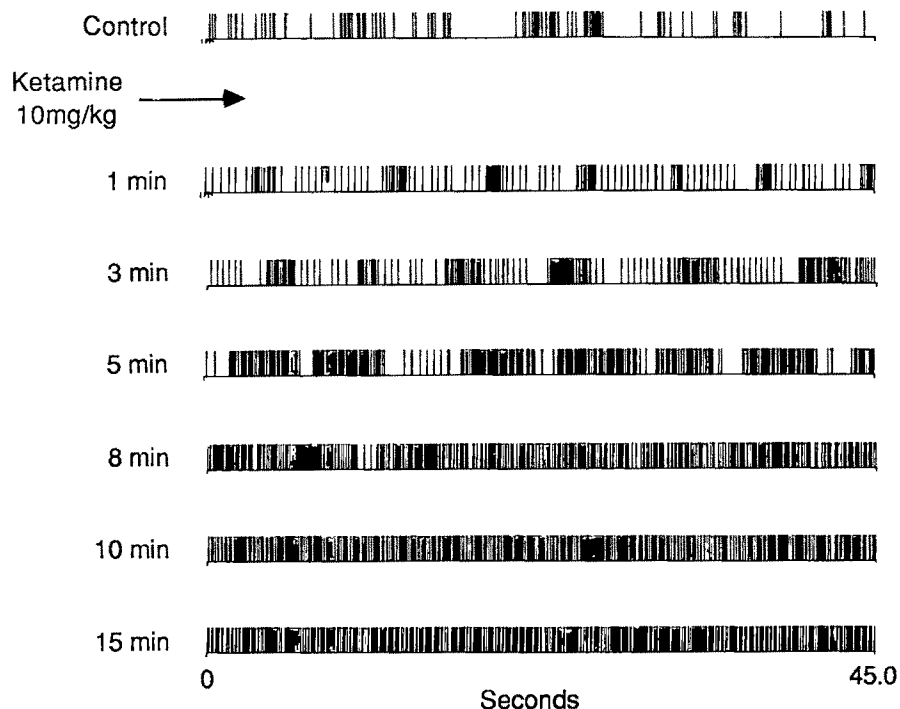


Figure 3. The effects of ketamine on the spontaneous activity of a single proprioceptive neuron. During control studies, the neuron fired in an irregularly spaced burst with a frequency of 2.6 events per second. One minute after 10 mg/kg of ketamine, the bursting activity became more regular and periodic in nature and increased to a rate of 5.6 events per second. As time progressed, the bursting activity became less apparent as the firing frequency increased until, at 15 min after ketamine, the cell was firing at a rate of 13.4 events/sec.

found to produce no significant change in the firing rate of that neuron.

In addition to changes in firing frequency induced in the proprioceptive neurons by the presence of ketamine, several cells were also found to have changes in the pattern of their spontaneous activity. Ketamine appeared to induce a periodic firing pattern that was not evident during control studies. Figure 3 demonstrates such a change in a neuron that was excited by 10 mg/kg of ketamine. This type of change in the periodic firing of the neurons was observed in five of the proprioceptive neurons recorded in this study.

Discussion

Before considering the implications of the results of this study, it is important to comment on the differences between the animal preparation used for these experiments and animal preparations used previously in studies of ketamine effects on dorsal horn neuronal activity. These animals were physiologically intact, awake, and drug-free prior to the administration of the test dose of ketamine. These facts mean that all of the normal physiologic modulation of spinal dorsal horn neuronal activity that would be expected to function in an intact animal should have been present and functioning in these animals. Normal function is particularly important when considering the effects of anesthetics and analgesics on the spinal dorsal horn,

because of the known descending modulatory factors that are capable of altering spinal dorsal horn neuron activity (6). In all of the acute preparations to date, these modulatory systems may have been significantly influenced by the preparation itself. Certainly, spinal cord transection will eliminate descending inhibitory control of spinal dorsal horn neurons. Decerebration is also likely to alter descending inhibitory systems. Anesthetics may influence spinal dorsal horn activity in at least two ways. First, and most obviously, anesthetics may act directly on the spinal neurons. In addition, because it has been proposed that anesthetics are capable of inhibiting inhibitory systems to a greater extent than excitatory systems, descending inhibitory modulation of spinal dorsal horn neuronal activity may be significantly altered by the presence of anesthetics. This report provides the first evidence of the effects of ketamine on spinal dorsal horn sensory transmission in an intact animal preparation where all of the systems that could be influenced by ketamine are present in the control situation. We can thus assume that any effect seen is similar to that occurring normally during ketamine anesthesia.

The ultimate question that this study was intended to address was whether or not the clear distinction that can be made between ketamine analgesia and anesthesia (7) is apparent at the spinal cord level. The results of this study suggest that, indeed, that is the case. These results indicate that the analgesic effect

of ketamine may be due, at least in part, to a spinal action upon noxious activity, whereas the anesthetic effect upon low threshold sensory input does not appear to involve an elimination of tactile sensory transmission at the spinal cord level. This conclusion was supported not only by the ability of the low threshold neurons to continue firing in the presence of anesthetic doses of ketamine, but also by the clear separation between inhibition of noxiously evoked activity of the neuron and lack of inhibition of low threshold evoked activity in the one WDR neuron which we were able to record. The recommended anesthetic dose of ketamine in cats is 8.8 mg/kg (8). Thus, the dose used in this study was slightly larger than the maximum recommended dose; in addition, in three low threshold neurons, an amount equal to twice that dose was used. In no instance was the depression of low threshold activity comparable to that seen in this study with WDR neurons, nor to that reported in other studies (1,2). A true dose-response study was not possible because of the excitatory phase caused in some animals by intravenous administration of subanesthetic doses.

The effects on the spontaneous activity of the proprioceptive neurons are in keeping with the observed behavioral effects of ketamine in both animals and humans. The tonic-clonic type of activity seen suggests that efferent motor activity is maintained intact and functional. The periodicity seen in several of the neurons in this study probably reflects the changes in muscle tension produced by the ability of ketamine to cause the tonic-clonic type of movement.

This study confirms earlier reports (1,2) of the separation of anesthesia and analgesia at the level of the spinal cord following ketamine administration and provides an opportunity for speculation on the likely site of action for the spinal analgesic effect of ketamine. The neurons from which we recorded were assumed to be second order or higher neurons. This is especially apparent for the wide dynamic range neurons, where input is received from several different kinds of primary afferent fibers. The input from the low threshold neurons does not appear to be significantly decreased by ketamine at anesthetic doses, which suggests that both the primary afferents carrying the information, as well as the interneurons responsible for communicating that information within the spinal dorsal horn, are not blocked by ketamine. These data also suggest that in the intact animal descending inhibition of LT spinal neurons is not enhanced by ketamine. On the contrary, the excitation of several LT neurons may be due to a removal of inhibitory factors on LT neurons. Thus, the ability of tactile somatosensory information to be dissociated

(as suggested by Corssen and Domino (3) and by the report (9) of a ketamine-induced decreased metabolism in the somatosensory system) by ketamine is dependent upon a site above the level of the spinal cord. The presence of intact, low threshold information to wide dynamic range neurons during blockade of noxiously evoked activity, as demonstrated in acute studies (1), gives evidence that the analgesic effects of ketamine may be selective for pain-transmitting systems and may involve either the primary afferents or the interneurons responsible for communicating that information to the WDR neuron. The importance of spinal sites for ketamine analgesia was demonstrated in a recent clinical report (10) of epidural use of ketamine for pain control. If the analgesia was a nonspecific depression of wide dynamic range neuron responses, then we should have seen a reduction in both the noxiously and nonnoxiously evoked activity. The maintenance of the nonnoxiously evoked activity indicates that either the specific transmitter systems associated with the noxious stimulus impinging upon the WDR neuron have been inhibited, or that synapses further out in the periphery are involved. Ketamine has been shown to selectively reduce excitation produced by specific neurotransmitters in the spinal cord (11).

The relative absence of neurons with a WDR response has been a constant finding in all of our studies of the intact spinal cord to date. This absence may reflect an important difference between acute and chronic preparations. Loss of descending inhibitory systems in the acute animal may unmask WDR responses that would normally be inhibited in the chronic (intact) preparation.

The ability to evaluate spinal cord sensory physiology and pharmacology in the intact animal has made it possible to confirm acute studies that pointed toward probable sites of action for ketamine anesthesia and analgesia. Future studies with other agents should help to provide better insight into the importance of spinal sites of action for the production of both anesthesia and analgesia.

The author wishes to express sincere gratitude to Ms. Ann Kerman-Hinds for her outstanding technical assistance without which this study would not have been possible, and to Ms. Linda Shiffrin for her professional and consistent manuscript preparation.

References

1. Conseiller C, Benoist JM, Hamann KF, Maillard MC, Besson JM. Effects of ketamine (CI 581) on cell responses to cutaneous stimulations in laminae IV and V in the cat's dorsal horn. *Eur J Pharmacol* 1972;18:346-52.

2. Kitahata LM, Taub A, Kosaka Y. Lamina-specific suppression of dorsal-horn unit activity by ketamine hydrochloride. *Anesthesiology* 1973;38:4-11.
3. Corssen G, Domino EF. Dissociative anesthesia: further pharmacologic studies and first clinical experience with the phencyclidine derivative CI-581. *Anesth Analg* 1966;45:29-40.
4. Collins JG. A technique for chronic extracellular recording of neuronal activity in the dorsal horn of the lumbar spinal cord in drug-free, physiologically intact cats. *J Neurosci Meth* 1985;12:277-87.
5. Wall PD. The laminar organization of dorsal horn and effects of descending impulses. *J Physiol (London)* 1967;188:403-24.
6. Basbaum AI, Fields HL. Endogenous pain control systems: brainstem spinal pathways and endorphin circuitry. In: Cowan WM, Shooter EM, Stevens CF, Thompson RF, eds. *Annual review of neuroscience*. Palo Alto: Annual Reviews, 1984;7:309-38.
7. Sacove MS, Shulman M, Hatano S, Fevold N. Analgesic effects of ketamine administered in subdissociative doses. *Anesth Analg* 1971;50:452-7.
8. Lamb WV, Jores EW. *Veterinary anesthesia*. Philadelphia: Lea and Febiger, 1973:322-3.
9. Crosby G, Crane AM, Sokoloff L. Local changes in cerebral glucose utilization during ketamine anesthesia. *Anesthesiology* 1985;56:437-43.
10. Islas J-F, Astorga J, Laredo M. Epidural ketamine for control of postoperative pain. *Anesth Analg* 1985;64:1161-2.
11. Anis NA, Berry SC, Burton NR, Lodge D. The dissociative anesthetics, ketamine and phencyclidine, selectively reduce excitation of central mammalian neurones by N-methyl-aspartate. *Br J Pharmacol* 1983;79:565-75.

Effects of Halothane and Decreased PO_2 on High Energy Phosphate Levels Maintained by Isolated Rat Liver Mitochondria

Gerald L. Becker, MD, David J. Miletich, PhD, and Ronald F. Albrecht, MD

BECKER GL, MILETICH DJ, ALBRECHT RF. Effects of halothane and decreased PO_2 on high energy phosphate levels maintained by isolated rat liver mitochondria. *Anesth Analg* 1986;65:1130-4.

Steady states of oxidative phosphorylation were achieved in mitochondrial suspensions continuously equilibrated with constant gas mixtures, simulating the conditions under which mitochondria contribute to the cellular energy status in vivo. The dependence of the mitochondria-maintained adenosine triphosphate/adenosine diphosphate (ATP/ADP) ratio on oxygen and halothane levels was examined at predetermined, clinically relevant concentrations of both gases. Inclusion of 1% halothane in the gas mixture decreased ATP/ADP by about half when mitochondrial respiration was

supported by NAD-linked substrate (glutamate); succinate-supported ATP/ADP was not inhibited. With either substrate, and whether or not 1% halothane was present, ATP/ADP was unaffected by decreases in PO_2 to values as low as 1.6 mm Hg. Under a range of typical in vivo conditions, therefore, 1% halothane significantly inhibited the mitochondrial contribution to steady state energy balance, whereas decreases in PO_2 did not. Combined effects of 1% halothane and reduced PO_2 on ATP/ADP were not seen, i.e., halothane did not increase the critical PO_2 level (hypoxic threshold) for inhibition of mitochondrial ATP production.

Key Words: ANESTHETICS, VOLATILE—halothane. METABOLISM—high energy phosphate. HYPOXIA—metabolism during.

Halothane and hypoxia each interfere with certain reactions of mitochondrial electron transport, the stepwise transfer of fuel-derived electrons to oxygen that releases sufficient energy to support the bulk of normal cellular ATP production (oxidative phosphorylation). As outlined schematically in Figure 1, halothane inhibits the enzyme nicotinamide adenine dinucleotide (reduced form) (NADH) dehydrogenase that represents the entry point for electrons into the respiratory chain (1-3). Hypoxia, on the other hand, prevents the exit of electrons from the chain by restricting the availability of oxygen. The combined effects of halothane and reduced PO_2 on the electron flow that supports mitochondrial energy production have not been examined. The importance of such a study is suggested by the occurrence of clinically significant cardiovascular depression and thus the potential for reduced oxygen delivery during halothane anesthesia (4,5). In tissues such as liver, the possibility

of impaired tissue oxygenation appears to be enhanced by anesthetic-mediated mechanisms that selectively decrease regional perfusion (6).

The assessment of mitochondrial energy generation under physiologic conditions is technically formidable. Intact tissues are heterogeneous with respect to ambient PO_2 , and the respective contributions of energy production and energy utilization to overall energy metabolism are difficult to resolve (7,8). These drawbacks are eliminated when isolated mitochondria are used for the study of oxidative phosphorylation. However, the standard practice of incubating mitochondrial suspensions in sealed chambers does not represent a realistic model of energy production in vivo: typically, concentrations of oxygen and high energy phosphates (HEP) are deliberately displaced from physiologic values to simplify reaction kinetics and thereby obtain constant rates of oxygen consumption. In vivo, on the other hand, mitochondrial energy generation operates much closer to equilibrium conditions, with the rate of oxidative phosphorylation restricted by the availability of substrates adenosine diphosphate (ADP) and (potentially) oxygen and by the accumulation of product (adenosine triphosphate, ATP) (9). Consequently, cellular energy status is more accurately reflected by the levels of HEP maintained than by the rate of oxygen consumption

Presented in part at the 1984 ASA Annual Meeting, New Orleans, Louisiana

Received from the Department of Anesthesiology, Michael Reese Hospital and Medical Center, and the Pritzker School of Medicine, University of Chicago, Chicago, Illinois. Accepted for publication June 11, 1986.

Address correspondence to Dr. Becker, Department of Anesthesiology, Michael Reese Hospital and Medical Center, Chicago, IL 60616.

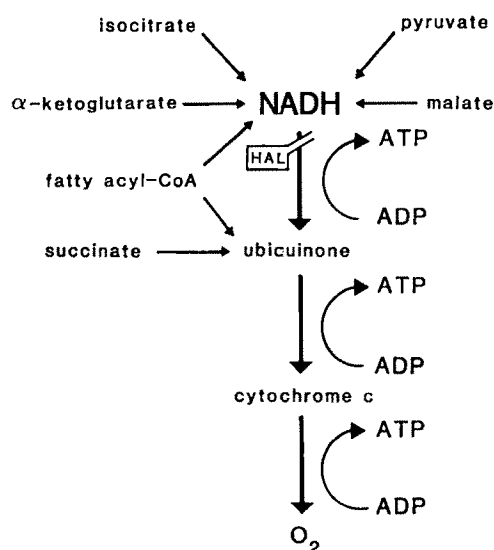


Figure 1. An outline of the principal reactions of mitochondrial respiration. Bold vertical arrows represent major segments of the respiratory (electron transport) chain within which energy released by electron transfers is coupled to energy-requiring ATP formation (oxidative phosphorylation). Lighter arrows represent donation of electrons to the chain via oxidations that occur during fatty acid and glucose (pyruvate) catabolism and the operation of the citric acid (Krebs) cycle. HAL designates the site of halothane inhibition of the respiratory chain (NADH dehydrogenase).

(8,10). In the work reported here, isolated mitochondria were incubated in an open system that permitted steady states of oxygen consumption and HEP metabolism to be attained at known, clinically relevant values of PO_2 and % halothane. The associated ATP/ADP ratios were then measured as an index of the efficacy of mitochondrial oxidative phosphorylation in maintaining extramitochondrial energy reserves.

Methods

Mitochondrial fractions were isolated from the livers of 23 adult female Sprague-Dawley rats using standard techniques of homogenization and differential centrifugation (11). Mitochondrial quality was checked by measuring ADP control of respiration (stimulation of oxygen consumption by added ADP) at 37°C in a sealed chamber with a built-in polarographic oxygen electrode (12).

Bioenergetic steady states were attained and analyzed by means of an approach described previously for use with isolated hepatocytes (13). Mitochondria were suspended in a medium resembling liver cytosol with regard to pH, ionic and osmotic strength, and concentrations of substrates and cofactors required for oxidative phosphorylation. The complete incubation mixture contained 120 mM KCl, 25 mM 4-(2-hydroxy-

ethyl)-1-piperazine ethanesulfonic acid (HEPES), 4 mM $MgCl_2$, 3 mM ATP, 0.1 mM ADP, 2 mM phosphate, either 2 mM/1 mM glutamate-malate or succinate, 2 mM, and mitochondria (2 mg protein/ml). The mitochondrial suspension (1.2 ml) was transferred to the oxygen electrode chamber (2.0 ml) mentioned above. The chamber was left uncapped and a continuous stream of humidified nitrous oxide-oxygen with or without 1% halothane, which was generated by an anesthesia machine, was directed down through the open top of the chamber onto the surface of the magnetically stirred suspension. The PO_2 in the suspension was monitored continuously by oxygen electrode, and halothane levels were checked intermittently by gas chromatography. Within about 5 min, steady states of oxygen metabolism developed, as indicated by the stabilization of the suspension PO_2 at a constant value. Preliminary studies confirmed that the PO_2 readings were not altered by the presence of halothane and that HEP values stabilized in parallel with the FO_2 (data not shown). At this point, the nitrous oxide-oxygen of the gas mixture was adjusted empirically to bring the suspension PO_2 to a predetermined constant value of 32, 16, 8, or 1.6 mm Hg. After 10 min of further incubation, metabolic activity was quenched by injecting 0.5 ml of 0.3N perchloric acid. The mixture was centrifuged to remove precipitated protein and neutralized with 0.5 M potassium hydroxide. The resulting clear extracts were analyzed enzymatically for ATP and ADP concentrations (14), and the corresponding ATP/ADP ratios calculated. The ratio ATP/ADP is an accepted measure of the balance between ATP production and utilization in various other systems, both in vivo and in vitro, which embody steady states of energy metabolism (7,8,15).

Groups of ATP/ADP values obtained at the four different PO_2 levels ($n = 23-30$ per group) were compared statistically using one-way analysis of variance. This comparison was carried out separately for measurements made in the presence and absence of halothane. At each specific value of PO_2 , ATP/ADP values measured in the presence and absence of halothane were compared with each other by use of the *t*-test for paired observations. In two subgroups of mitochondrial preparations, ATP/ADP was measured both in the presence and absence of halothane and at each of the two lowest PO_2 values (1.6 and 8 mm Hg) for each preparation studied. In one subgroup ($n = 14$), glutamate-malate was the substrate; in the other ($n = 8$), the substrate was succinate. In these two subgroups, the dependence of ATP/ADP on PO_2 as well as on halothane could therefore be examined by use of paired *t*-testing thereby eliminating variation caused by differences in ATP/ADP "baselines" com-

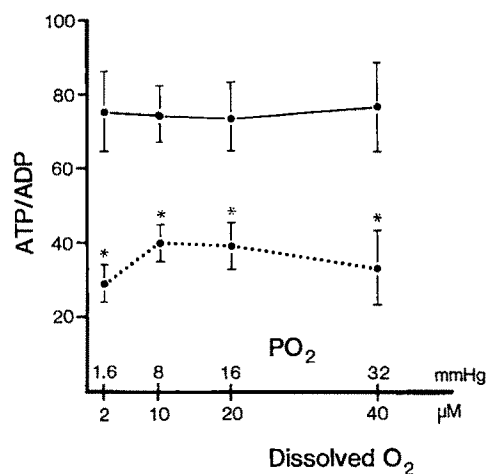


Figure 2. Steady state values of ATP/ADP (mean \pm SEM) in mitochondrial suspensions as a function of medium PO₂ and dissolved oxygen concentration at 37°. Solid lines connect values obtained in the absence of halothane; dotted lines connect values obtained with 1% halothane present.

monly seen among different mitochondrial preparations. $P < 0.05$ was considered significant.

Results

Values of steady state ATP/ADP in mitochondrial suspensions using glutamate-malate as respiratory substrate are plotted as a function of steady state oxygen levels in Figure 2. Oxygen levels are given in units of both PO₂ (mm Hg) and the equivalent dissolved oxygen concentration (μ M) at 37°C. The introduction of 1% halothane produced a statistically significant decrease in ATP/ADP which was comparable in extent (down to approximately 50% of the control value) at all four PO₂ values examined. With halothane absent, ATP/ADP showed no dependence on PO₂ down to values as low as 1.6 mm Hg. With halothane present, ATP/ADP did show a PO₂-related decrease at the lowest PO₂ value (1.6 mm Hg), but this decrease was not significant either by analysis of variance across all PO₂ values or by *t*-test comparison with the value of ATP/ADP at the next highest PO₂ (8 mm Hg).

Even for the subgroup of experiments ($n = 14$) in which PO₂ effects on ATP/ADP could be examined by paired analysis to eliminate confounding variation reflecting differences between mitochondrial preparations (Table 1), differences in ATP/ADP between the two lowest PO₂ values with halothane present failed to achieve statistical significance. Differences attributable to the presence/absence of halothane at each individual PO₂ remained significant. Table 1 also shows that with succinate as respiratory substrate ($n = 8$), ATP/ADP values obtained were comparable to those

Table 1. Steady State ATP/ADP Values in Mitochondrial Suspensions

Substrate	Halothane	PO ₂ (mm Hg)	
		1.6	8
Glutamate ($n = 14$)	—	61 \pm 9	57 \pm 8
	+	23 \pm 5 ^a	33 \pm 8 ^a
Succinate ($n = 8$)	—	44 \pm 9	59 \pm 14
	+	26 \pm 6	37 \pm 10

Values given are means \pm SEM

^aDifferent from —halothane at $P < 0.05$ by paired *t*-test corrected for multiple applications.

with glutamate-malate. In the case of succinate, however, neither halothane- nor PO₂-related differences in ATP/ADP were significant.

Discussion

The goal of this study was to simulate the steady state conditions under which mitochondrial energy generation occurs in vivo and then to measure the effects of clinically relevant oxygen and halothane levels on a sensitive indicator of cellular energy status, the extramitochondrial ATP/ADP ratio. Observed values of this ratio were consistent with those reported by others under similar conditions (15,16). The ATP/ADP values measured in this study were substantially higher than those measured in intact tissue (7) because mitochondria contain most of the cell's ATP-producing activity although accounting for only a small portion of ATP utilization. This predominance of energy generation in mitochondrial suspensions magnifies this system's ability to respond to agents or manipulations that inhibit oxidative phosphorylation.

Halothane, at a clinically relevant concentration (1%), produced statistically significant ATP/ADP reductions in glutamate-malate-energized mitochondria. On the other hand, significant ATP/ADP decreases caused by halothane were not observed when mitochondrial respiration was supported by succinate. This result indicates that the observed effects of halothane are attributable specifically to the latter's action on electron flow in the NADH dehydrogenase region of the respiratory chain, because it is only in this regard that the reactions of glutamate- and succinate-supported respiration are different (see Fig. 1).

These findings also constitute the first direct demonstration that halothane inhibition of NAD-mediated mitochondrial oxidations impairs the ability of mitochondria to maintain HEP levels under physiologically realistic steady state conditions. The clinical implication of this result resides in the fact that despite the existence of alternative pathways for substrates

(e.g., succinate) to donate electrons to the respiratory chain, the bulk of oxidative energy generation in intact liver is supported by electron transfers which are NAD-mediated and thereby subject to inhibition at the NADH dehydrogenase step (7).

The contrasting lack of ATP/ADP dependence on PO_2 is also consistent with previous work. Mitochondrial electron transport was found to have a very high affinity for oxygen such that the rate of oxidative phosphorylation becomes oxygen-limited only at PO_2 values below 1 mm Hg (17). The PO_2 effects on ATP/ADP were thus negligible over the broad range of intracellular PO_2 values which would normally prevail *in vivo*. The highest PO_2 examined in this study was close to the estimated average extracellular PO_2 in intact liver (18), whereas the lowest PO_2 was just slightly higher than the so-called "critical PO_2 " for isolated mitochondria (1 mm Hg), below which the rate of oxidative phosphorylation becomes limited by the availability of oxygen (17,18). Measurements of mitochondrial energy generation within the PO_2 -limited (i.e., hypoxic) range in this study were precluded by the inability to accurately stabilize and measure PO_2 at values between 0 and 1 mm Hg. Thus, the bioenergetic consequences of having oxidative phosphorylation simultaneously halothane- and oxygen-limited could not be examined directly in this study. However, because the immediately adjacent, extreme lower end of the normoxic PO_2 range was attained, the possibility that halothane and hypoxia interacted or combined in the production of energy deficits can be ruled out: the presence of 1% halothane did not significantly reduce ATP/ADP values at the extreme lower end of the normoxic range ($PO_2 = 1.6$ mm Hg) compared to ATP/ADP at higher PO_2 (Fig. 2). In other words, 1% halothane did not raise the hypoxic threshold (critical PO_2) for mitochondrial ATP production.

Although not specifically addressed in this study, the effects reported for halothane on energy generation by liver mitochondria may well be applicable to other anesthetics and other tissues. Other inhalational anesthetics have also been shown to inhibit liver mitochondrial respiration *in vitro* in direct proportion to their anesthetic potency (19). Furthermore, halothane has been reported to inhibit oxygen consumption (electron transport) in mitochondria from brain (20) and skeletal muscle (21); and in general the mitochondrial literature shows little evidence for differences among tissues in their response to various electron transport inhibitors.

Finally, this study has deliberately excluded other factors well known to affect cellular energy status *in vivo*, such as compensatory ATP production via anaerobic glycolysis and parallel anesthetic inhibition of

energy-using processes (7,8,22). The extent to which anesthetic effects on these other processes interact with the effects on mitochondrial energy generation reported herein remains an important topic for future experiments.

The authors are grateful to Michael Morgan, Audrey Holland and Anthony Sharp for their expert technical assistance and to Sherry Amon for her help with the manuscript.

References

- 1 Cohen PJ, Marshall BE. Effects of halothane on respiratory control in rat liver mitochondria. In: Fink BR, ed. Toxicity of anesthetics. Baltimore: Williams and Wilkins, 1968:24-36.
- 2 Miller RN, Hunter FE. The effect of halothane on electron transport, oxidative phosphorylation, and swelling in rat liver mitochondria. *Mol Pharmacol* 1970;6:67-77.
- 3 Harris RA, Munroe J, Farmer B, Kim KC, Jenkins P. Action of halothane upon mitochondrial respiration. *Arch Biochem Biophys* 1971;42:435-44.
- 4 Epstein RM, Deutsch S, Cooperman LH, Clement AJ, Price HL. Splanchnic circulation during halothane anesthesia and hypercapnia in normal man. *Anesthesiology* 1966;27:654-61.
- 5 Thulin L, Andreen M, Irestedt L. Effect of controlled halothane anesthesia on splanchnic blood flow and cardiac output in the dog. *Acta Anesthesiol Scand* 1975;19:146-53.
- 6 Gelman S, Fowler KC, Smith LR. Regional blood flow during isoflurane and halothane anesthesia. *Anesth Analg* 1934;63:557-65.
- 7 Biebuyck JF, Lund P, Krebs HA. The effects of halothane on glycolysis and biosynthetic processes of isolated perfused rat liver. *Biochem J* 1972;128:711-20.
- 8 Siesjö BK. Brain energy metabolism. New York: Wiley & Sons, 1978:256-7.
- 9 Davis EJ, Davis-van Thienen WIA. Rate control of phosphorylation-coupled respiration by rat liver mitochondria. *Arch Biochem Biophys* 1984;233:573-81.
- 10 Erccinska M, Wilson DF. Regulation of cellular energy metabolism. *J Membr Biol* 1982;70:1-14.
- 11 Johnson D, Lardy H. Isolation of liver or kidney mitochondria. In: Estabrook RW, Pullman ME, eds. Oxidation and phosphorylation. New York: Academic Press, 1967:94-6. (Colowick SP, Kaplan NO, eds. Methods in enzymology; vol. X).
- 12 Estabrook RW. Mitochondrial respiratory control and the polarographic measurement of ADP:O ratios. In: Estabrook RW, Pullman ME, eds. Oxidation and phosphorylation. New York: Academic Press, 1967:41-7. (Colowick SP, Kaplan NO, eds. Methods in enzymology; vol. X).
- 13 Becker GL, Hensel P, Holland AD, Miletich DJ, Albrecht RF. Energy deficits in hepatocytes isolated from phenobarbital-treated or fasted rats and briefly exposed to halothane and hypoxia *in vitro*. *Anesthesiology*, in press.
- 14 Bergmeyer HU. Methods of biochemical analysis. New York, Academic Press, 1974:2097-127.
- 15 Wanders RJA, van den Berg GB, Tager JM. A re-evaluation of conditions required for an accurate estimation of the extramitochondrial ATP/ADP ratio in isolated rat liver mitochondria. *Biochim Biophys Acta* 1984;767:113-9.
- 16 Davis EJ, Lumeng L. Relationships between the phosphorylation potentials generated by liver mitochondria and respi-

- ratory state under conditions of ADP control. *J Biol Chem* 1975;250:2275-82.
17. Wilson DF, Owen CS, Erecinska M. Quantitative dependence of mitochondrial oxidative phosphorylation on oxygen concentration: a mathematical model. *Arch Biochem Biophys* 1979;195:485-93.
 18. Rosenberg H, Haugaard N. The effects of halothane on metabolism and calcium uptake in mitochondria of the rat liver and brain. *Anesthesiology* 1973;39:44-53.
 19. Nahrwold ML, Cohen PJ. The effects of Forane and fluroxene on mitochondrial respiration: correlation with lipid solubility and in vivo potency. *Anesthesiology* 1973;38:437-44.
 20. Cohen PJ. The metabolic function of oxygen and biochemical lesions of hypoxia. *Anesthesiology* 1972;37:148-77.
 21. Britt BA, Kalow W, Endrenyi L. Effects of halothane and methoxyflurane on rat skeletal muscle mitochondria. *Biochem Pharmacol* 1972;21:1159-69.
 22. Merin RG, Kumazawa T, Luka NL. Myocardial function and metabolism in the conscious dog and during halothane anesthesia. *Anesthesiology* 1976;44:402-15.

Intermittent Positive Pressure Ventilation with either Positive End-Expiratory Pressure or High Frequency Jet Ventilation (HFJV), or HFJV Alone in Human Acute Respiratory Failure

J. F. Brichant, MD, J. J. Rouby, MD, and P. Viars, MD

BRICHANT JF, ROUBY JJ, VIARS P. Intermittent positive ventilation with either positive end-expiratory pressure or high frequency jet ventilation (HFJV), or HFJV alone in human acute respiratory failure. *Anesth Analg* 1986;65:1135-42.

Continuous Positive Pressure Ventilation (CPPV), High-Frequency Jet Ventilation (HFJV), and a combination of HFJV with Intermittent Positive Pressure Ventilation (CV) were randomly compared in 13 critically ill patients with severe acute respiratory failure. Ventilatory settings were chosen in order to apply the same mean airway pressure (P_{aw}) during the three modes. Respiratory frequencies were adjusted during CPPV (16 ± 2 breaths/min) and HFJV (235 ± 32 breaths/min) to achieve the same level of P_{aCO_2} and were then combined during CV. All patients were heavily sedated during the study and had had peripheral and balloon-tipped pulmonary arterial catheters previously inserted. After a steady state at F_{IO_2} 1 in each mode of ventilation, hemodynamic and respiratory parameters were measured. A P_{aw} of 13.8 ± 2.9 mm Hg was applied to each

patient by using a PEEP of 7.4 mm Hg during CPPV; a driving pressure of 2.9 ± 0.2 bars and an I/E ratio of 0.43 during HFJV; and by combining HFJV, using a driving pressure of 1.2 ± 0.3 bars with intermittent positive pressure ventilation during CV. There were no significant differences in any of the hemodynamic or respiratory parameters measured, except for a significant decrease in P_{aCO_2} during CV when compared to CPPV or HFJV. We concluded that 1) arterial oxygenation and cardiac output depend mainly on P_{aw} independent of the method used to increase P_{aw} and 2) CV can improve CO_2 elimination without increasing P_{aw} . Because this latter advantage can also be obtained by using HFJV, we were unable to demonstrate any decisive advantage for this form of CV sufficient to recommend this rather complicated and expensive type of ventilation as the primary mode of ventilatory support in acute with severe acute respiratory failure.

Key Words. VENTILATION—high frequency jet and intermittent positive pressure.

It is well-established that both continuous positive pressure ventilation (CPPV) and high-frequency jet ventilation (HFJV) improve arterial oxygenation in patients with acute respiratory failure through an increase in functional residual capacity (1,2). When HFJV and CPPV administered at random to a large series of critically ill patients with acute respiratory failure were compared, no significant advantage could be found for either technique (3). One explanation for this result may be the lack of homogeneity of etiology for the cases of respiratory failures studied. In fact, HFJV is superior to CPPV for certain forms of acute respiratory failure. Patients with large bronchopleural fistulae or tracheoesophageal lesions leading to pro-

gressive deterioration of gas exchange with CPPV can be markedly improved by HFJV (4-7). Patients in acute respiratory failure associated with circulatory shock have better hemodynamic function when ventilated with HFJV than when ventilated with CPPV at identical levels of mean airway pressure (P_{aw}) and P_{aCO_2} (8). HFJV with superimposed spontaneous breathing can achieve better gas exchange than CPPV can in patients with mild postoperative respiratory failure (9).

However, some severe forms of acute respiratory failure do not respond to either CPPV or HFJV. A recent study has suggested that the combination of high-frequency oscillatory ventilation with intermittent mandatory ventilation (HFOV-IMV) could improve gas exchange in neonates with acute respiratory failure characterized by severe hypoxemia and CO_2 retention under conventional intermittent mandatory ventilation (CIMV) (10). Moreover, many teams using HFJV utilize it routinely in combination with intermittent positive pressure ventilation (IPPV) or CPPV.

Presented in part at the Annual Meeting of the American Society of Anesthesiologists, San Francisco, California, October 1985.

Received from the Département d'Anesthésie, Centre Hospitalo-Universitaire Pitié-Salpêtrière, Paris, France. Accepted for publication May 28, 1986.

Address correspondence to Dr. Rouby, Département d'anesthésie, CHU Pitié-Salpêtrière, 83 Boulevard de l'Hôpital, 75651 Paris Cédex 13, France.

Although reasons for this association are not completely clear, it has recently been suggested that superimposed high-frequency ventilation on conventional mechanical ventilation could improve ventilation perfusion homogeneity and, consequently, arterial oxygenation (11,12).

The aim of the present study was to determine whether the combination of HFJV and IPPV could improve gas exchange in patients with severe acute respiratory failure, when compared to CPPV alone or HFJV alone. Three modes of ventilatory support were studied: CPPV, HFJV, and a combination of HFJV with IPPV(CV).

Methods

Patients

Thirteen critically ill patients admitted to the Surgical Intensive Care Unit of la Pitié Hospital for acute respiratory failure were selected for the study according to the following criteria: 1) radiological evidence of bilateral alveolar infiltrates; 2) $\text{PaO}_2 < 250$ mm Hg (IPPV, FiO_2 1); 3) static respiratory compliance < 65 ml/cm H_2O ; and 4) stable hemodynamic condition (mean arterial pressure > 70 mm Hg without inotropic support).

All patients with a past history of chronic obstructive pulmonary disease, asthma, or unilateral lung disease were excluded. All patients had previously inserted arterial cannulae and balloon-tipped pulmonary catheters for cardiovascular monitoring. Informed consent was obtained either from the patient or patient's closest relative, and authorization was given by the Clinical Investigation Committee of this Institution. Within the 24 hr preceeding the study, static respiratory compliance, alveolar dead space, and end-expiratory pressure gradient between end-diastolic pulmonary arterial pressure and capillary wedge pressure (EDPAP-PWP gradient) were measured during IPPV. Respiratory volume-pressure curves were recorded using a specially constructed 2-L syringe and X-Y recorder (Omnigraph Houston Instruments) as previously described (2). Static respiratory compliance was considered as the slope of the curve between 500 and 1000 ml on deflation limb. Alveolar dead space (V_{DA}) was calculated as $1 - \text{PACO}_2/\text{PaCO}_2$, where PACO_2 is end tidal alveolar carbon dioxide tension measured by a calibrated Hewlett-Packard CO_2 analyzer, and PaCO_2 is the arterial carbon dioxide tension simultaneously measured from an arterial blood sample. Because most acute respiratory failures are associated with pulmonary arterial occlusions by local

thrombi, V_{DA} is a better reflection of these vascular lesions than physiologic dead space. The EDPAP-PWP gradient, which is considered as a good indicator of acute respiratory failure severity (13), was measured from the pulmonary arterial catheter. Initial diagnosis and respiratory status during IPPV 24 hr before the beginning of the study are summarized in Table 1.

In 12 patients, CV was used only for the duration of the study. Throughout the course of their respiratory disease, six patients were ventilated using HFJV and six patients using CPPV during a mean time of 32 ± 28 days (mean \pm SD). Because of persistent hypercarbia during both HFJV and CPPV, patient 11 was ventilated with CV for 24 hr until she died.

Equipment

All patients were intubated with a HI-LO jetTM endotracheal tube (NCC, Division Mallinckrodt, Inc., Argyle, NY). This tube, previously used for high-frequency ventilation (10,14,15), is characterized by the presence of three separate channels:

1. The main channel (internal diameter in accordance with the size of the endotracheal tube) is used to deliver the total flow of gas or the entrainment during CPPV, HFJV, and CV.
2. The first auxiliary channel (2 mm internal diameter) is used as the "jet insufflation channel" during HFJV and CV. It ends 6 cm above the distal tip of the endotracheal tube. During CPPV, this channel is plugged.
3. The second auxiliary channel (1 mm internal diameter) is used as the airway pressure monitoring channel. It ends 1 cm above the distal tip of the endotracheal tube. Consequently, airway pressure was measured 5 cm below the outlet of the jet insufflation channel. In a preliminary study, we verified the accuracy of measuring mean airway pressure (P_{aw}) through this channel. A catheter ending 10 cm below the outlet of the jet insufflation channel was introduced in the trachea, and P_{aw} measured from this catheter was compared with P_{aw} measured from the airway pressure monitoring channel in three consecutive patients. In each individual, the difference between the two measurements never exceeded 1 mm Hg. Therefore the airway pressure monitoring channel of the HI-LO endotracheal tube was considered adequate for measuring P_{aw} .

CPPV was administered using an Ohmeda CPU 1 ventilator (Ohmeda Maurepas, France) connected to the main channel of the HI-LO jet endotracheal tube. Gases were heated and humidified using a Fisher

Table 1. Characteristics of Patients before the Study (IPPV, FI_{O_2} 1)

Patient	Sex	Weight (kg)	Age	Initial diagnosis	Outcome ^a	Pulmonary failure	Static respiratory compliance ml/cm H ₂ O	Qs/Qt (%)	V _D A (%)	EDPAP-PWP gradient	PaO ₂ mm Hg	PaCO ₂ mm Hg	(A-a)DO ₂	Vt (ml/kg)	Frequency breaths/min
1	M	56	20	Multiple trauma	D	Bacterial pneumonia	40	25	40	6	202	35	476	16	19
2	F	59	21	Multiple trauma	D	Bacterial pneumonia	40	28	—	6	200	42	471	12	20
3	M	63	44	Multiple trauma	S	Bacterial pneumonia	45	32	29	6	182	37	494	14	16
4	F	58	69	Endarterectomy	S	Cardiogenic pulmonary	50	25	—	3	98	32	583	14	14
5	F	49	79	Peritonitis	D	Bacterial pneumonia	40	28	—	5	174	37	524	19	15
6	M	82	51	Perinephric hematoma	D	Bacterial pneumonia	44	55	26	5	47	43	623	15	16
7	M	61	33	Multiple trauma	S	Bacterial pneumonia	41	32	18	8	179	35	499	14	16
8	M	75	39	Multiple trauma	S	Pulmonary contusion	50	30	37	7	160	33	520	13	15
9	M	78	39	Multiple trauma	S	Pulmonary contusion	35	28	30	3	215	39	459	12	15
10	M	140	56	Pickwickian syndrome	D	Cardiogenic pulmonary edema	48	36	15	6	65	37	611	9	15
11	F	45	57	Esophago-gastrectomy	D	Bacterial pneumonia	47	33	40	13	90	57	566	22.9	20
12	F	180	57	Pickwickian syndrome	S	Bacterial pneumonia	60	20	—	9	170	35	508	5	15
13	F	109	76	Miller-Fisher syndrome	S	Bacterial pneumonia	65	20	17	10	170	31	512	9	15
Mean ± SD	—	81 ± 40	49 ± 19	—	—	—	46 ± 8	30 ± 9	28 ± 10	6.7 ± 2.8	150 ± 55	38 ± 6.7	526 ± 53	13 ± 4	16 ± 2

^aS, survived; D, died.

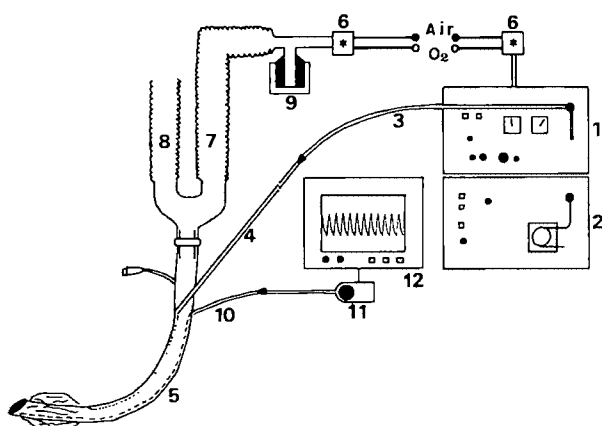


Figure 1. Circuit for high-frequency jet ventilation. Labels: 1, VS 600 S Ventilator; 2, Acutronic HH-812 heater and humidifier; 3, connecting tube; 4, Jet insufflation channel; 5, HI-LO endotracheal tube; 6, blender; 7, bias flow; 8, expiratory line; 9, Fischer Paykel 328 humidifier; 10, airway pressure monitoring channel; 11, low pressure quartz transducer; 12, continuous monitoring of airway pressure.

Paykel 328 Humidifier (Fisher and Paykel Ltd, New Zealand).

HFJV (Fig. 1) was delivered using an Acutronic VS 600 S ventilator (Acutronic Medical Systems, Switzerland) connected to the jet insufflation channel of the HI-LO endotracheal tube. Injected gases were heated and humidified using an Acutronic HH-812 heater and humidifier (Acutronic Medical Systems, Switzerland). A roller pump injected 20°C distilled water in a heating chamber, which generated 110°C vapor. This vapor was then delivered in the jet stream close to the solenoid valve. Injected gases along the connecting tube were maintained heated by four electrical resistances located in the wall of the connecting tube. Finally, gases were delivered in the trachea at a temperature between 36 and 37°C. To obtain 100% relative humidity at 37°C, water injection rate (ml/hr) was set according to the following formula (16):

$$\text{Water injection rate (ml/hr)} = 2.64 V_{\text{inj}} (\text{L/min})$$

where V_{inj} is the flow of gas delivered by the jet ventilator, which can be easily measured using a water sealed spirometer. Gas for entrainment was provided via a 3-way swivel adapter connected to the main channel of the HI-LO endotracheal tube, using an open anesthesia circuit delivering a continuous bias flow of gas (20 L/min). Entrained gases were heated and humidified using a Fisher Paykel 328 humidifier and set at the same FI_{O_2} as injected gases.

Combined ventilation (HFJV + IPPV, Fig. 2) was delivered by connecting the Ohmeda CPU 1 ventilator to the main channel of the HI-LO endotracheal tube

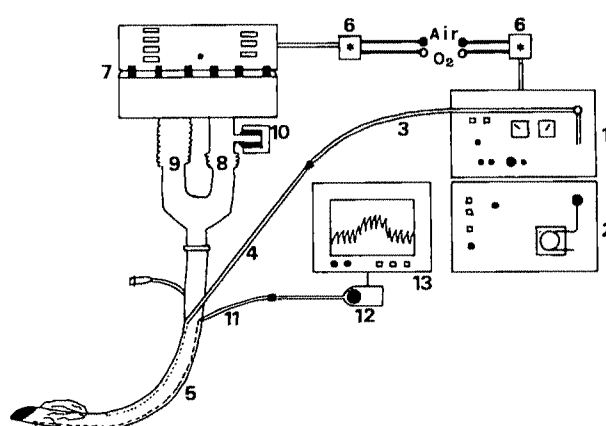


Figure 2. Circuit for combined ventilation. 1, VS 600 S Ventilator; 2, Acutronic HH-812 heater and humidifier; 3, connecting tube; 4, Jet insufflation channel; 5, HI-LO endotracheal tube; 6, blender; 7, Ohmeda CPU 1 ventilator; 8, inspiratory line of the conventional ventilator; 9, expiratory line of the conventional ventilator; 10, Fisher Paykel 328 humidifier; 11, airway pressure monitoring channel; 12, low pressure quartz transducer; 13, continuous monitoring of airway pressure.

and by simultaneously connecting the Acutronic VS 600 S ventilator to the jet insufflation channel.

In each mode, airway pressure was continuously monitored using a low pressure calibrated quartz pressure transducer (Hewlett-Packard 1290 A) filled with air and connected to the airway pressure monitoring channel of the HI-LO endotracheal tube. The frequency response of the tubing and transducer was 5 Hz. Because of this low frequency response, we were unable to accurately measure minimum and maximum airway pressure. P_{aw} was obtained by electronic damping of the signal.

Procedures

Each patient received the three modes of ventilation at random. Ventilatory parameters were chosen in order to achieve the same level of P_{aw} . P_{aw} was fixed in order to obtain at least a 30% increase in PaO_2 (FI_{O_2} 1) as compared with IPPV.

During CPPV, a PEEP of 10 cm H_2O was applied, and I/E ratio was set to 0.43. Tidal volume and frequency were adjusted to obtain the desired level of P_{aw} . This was easy to realize, because any change in tidal volume or frequency induced a wide variation in insufflation pressures in these patients with decreased respiratory compliance.

During HFJV, I/E ratio was maintained constant at 0.43, and driving pressure was adjusted to obtain the desired level of P_{aw} . Respiratory frequency was set to get the same PaCO_2 as that during CPPV.

During CV, the same ventilatory settings used for

Table 2. Respiratory Data According to the Mode of Ventilation (mean \pm SD)

	I/E	Frequency (beats/min)	Driving pressure (bars)	VT (ml/kg)	PEEP (mm Hg)	P_{aw} (mm Hg)	P_{aw} -RAP (mm Hg)	P_{aO_2} (mm Hg) (F_{iO_2} 1)	Qs/Qt (%)	(A-a)DO ₂ (mm Hg)	Paco ₂ (mm Hg)
CPPV	0.43	16 \pm 2	—	14 \pm 4	7.4	13.8 \pm 2.9	4.3 \pm 3.3	252 \pm 81	25 = 8	414 \pm 84	41.5 \pm 6.2
HFJV	0.43	253 \pm 32	2.9 \pm 0.2	NM ^a	—	13.8 \pm 2.9	4.1 \pm 3.6	263 \pm 76	24.2 = 5.5	411 \pm 74	42 \pm 8.2
CV											
IPPV	0.43	16 \pm 2	—	14 \pm 4	0	13.8 \pm 2.9 ^b	3.6 \pm 3.9	252 \pm 80	23.9 \pm 5.3	432 \pm 78	32.8 \pm 6.5 ^b
HFJV	0.43	235 \pm 32	1.2 \pm 0.3	NM ^a							

^aNM, Not measured.^bP < 0.05 CV vs CPPV or HFJV.

CPPV and HFJV were combined, but PEEP was suppressed and driving pressure was adjusted to obtain the desired level of P_{aw} .

In each mode of ventilation, after a steady state of 20 min at F_{iO_2} 1, mean right atrial pressure (RAP), mean pulmonary arterial pressure (MPAP), mean pulmonary wedge pressure (PWP), mean arterial pressure (MAP), heart rate (HR), and cardiac output were measured. Cardiac output was measured using the thermodilution technique and a bedside computer (Hewlett-Packard 78231 C). Three injections of iced 5% dextrose in water were made at different moments of the ventilatory cycle to average the variations in cardiac output due to intrathoracic pressure swings during inspiratory and expiratory phases. Cardiac index (CI), stroke index (SI), systemic vascular resistance (SVR), pulmonary vascular resistance (PVR) were calculated using the following formulas

$$CI (L \cdot \min^{-1} \cdot m^{-2}) = \frac{\text{Cardiac output (L/min)}}{\text{Body surface (m}^2\text{)}}$$

$$SI (ml/m^2) = \frac{CI (ml \cdot \min^{-1} \cdot m^{-2})}{HR (beat/min)}$$

$$SVR (IU/m^2) = \frac{MAP - RAP}{CI}$$

$$PVR (IU/m^2) = \frac{MPAP - PWP}{CI}$$

Central mixed venous blood and arterial blood were sampled for blood gas analysis within 1 min after cardiac output measurements. P_{aO_2} , $P\bar{V}_{O_2}$, P_{aCO_2} , and pH were determined using an IL 1302 (Instruments Laboratories). Mixed venous oxygen saturation ($S\bar{V}_{O_2}$), arterial and venous hemoglobin (Hba, Hbv) were measured using a Cooxymeter OSM 2 (Instruments Laboratories). Arterial, venous, and capillary oxygen contents (CaO_2 , $C\bar{V}_{O_2}$, CCO_2), pulmonary shunt (Qs/Qt), arteriovenous oxygen difference ($C_{(a-v)O_2}$), and oxygen consumption (\dot{V}_{O_2}) were calculated as follows:

$$CaO_2 (ml/100 ml) = (1.34 \times Hba \times SaO_2) + 0.003 PaO_2$$

$$C\bar{V}_{O_2} (ml/100 ml) = (1.34 \times Hbv \times S\bar{V}_{O_2}) + 0.003 P\bar{V}_{O_2}$$

$$CCO_2 (ml/100 ml) = (1.34 \times Hb) + (0.003 \times (713 - PaCO_2))$$

$$Qs/Qt (\%) = \frac{CCO_2 - CaO_2}{CCO_2 - C\bar{V}_{O_2}}$$

$$C_{(a-v)O_2} (vol/100 ml) = CaO_2 - C\bar{V}_{O_2}$$

$$\dot{V}_{O_2} (ml \cdot \min^{-2} \cdot m^{-2}) = C_{(a-v)O_2} \times CI$$

After recording hemodynamic variables, P_{aw} was measured, and the difference between P_{aw} and RAP was calculated. Variations in this difference were considered a good approximation of transpulmonary pressure variations, because P_{aw} and fluid loading were carefully controlled throughout the study. In order to take into account the simultaneous changes in P_{aCO_2} when interpreting any change in P_{aO_2} , alveoloarterial difference in oxygen pressure (A - a) DO₂ was calculated using the simplified alveolar gas equation:

$$(A - a) DO_2 (mm Hg) = PB - PaCO_2 - PaO_2 - 47$$

where PB is atmospheric pressure.

Statistical Analysis

All data were expressed as mean \pm SD and compared using a two-way analysis of variance completed by a modified Student's *t*-test; *P* < 0.05 was considered statistically significant.

Results

Respiratory data in the three modes of ventilation are summarized in Table 2. A P_{aw} of 13.8 \pm 2.9 mm Hg was applied in each mode. This was obtained 1) during CPPV by using an I/E ratio of 0.43, a tidal volume of 14 \pm 4 ml/kg, a frequency of 16 \pm 2 breaths/min, and a PEEP of 7.4 mm Hg; 2) during HFJV, by using a I/E ratio of 0.43 and a driving pressure of 2.9 \pm 0.2 bars; 3) during CV by suppressing PEEP and by de-

Table 3. Hemodynamic Data in the Three Modes of Ventilation (mean \pm SD)

	MAP (mm Hg)	CI (L·min ⁻¹ ·m ⁻²)	HR (beats/min)	SI (ml·m ⁻²)	$\dot{V}O_2$ (ml·min ⁻¹ ·m ⁻²)	C(a-v)O ₂ (vol/100 ml)	SVR (IU/m ²)	PVR (IU/m ²)	RAP (mm Hg)	MPAP (mm Hg)	PWP (mm Hg)
CPPV	89 \pm 11	4.4 \pm 1.4	104 \pm 26	42 \pm 10	196 \pm 80	4.6 \pm 1.3	20 \pm 6	4.2 \pm 2.3	9.3 \pm 3.5	28 \pm 6	13.5 \pm 4.3
HFJV	89 \pm 9	4.5 \pm 1.2	105 \pm 25	43 \pm 8	198 \pm 55	4.3 \pm 0.9	18 \pm 6	3.7 \pm 2	9.5 \pm 3.0	28 \pm 6	14 \pm 2.8
CV	84 \pm 10	4.2 \pm 1.3	99 \pm 26	42 \pm 8	192 \pm 54	4.8 \pm 1	19 \pm 5	3.4 \pm 1.8	10 \pm 4	32 \pm 17	13.9 \pm 4.3

creasing the driving pressure of the HFJV component to 1.2 ± 0.3 bars. Using these ventilatory settings, PaCO₂ was significantly lower during CV as compared with HFJV and CPPV. In contrast, PaO₂, Qs/Qt, and the difference between P_{aw} and RAP were not significantly different. In 11 patients (A - a)DO₂ was higher during HFJV than CV and in 10 patients, (A - a)DO₂ was higher during CPPV than CV. However, these changes were not statistically significant.

Hemodynamic data in the three modes of ventilation are summarized in Table 3. There were no significant changes in any of the hemodynamic parameters measured during CPPV, HFJV and CV.

Discussion

In this study comparing CPPV, HFJV and the combination of HFJV and IPPV (CV) in patients with severe acute respiratory failure, we found that CV could enhance CO₂ elimination without increasing mean airway pressure. The hypothesis that HFJV superimposed on the conventional respiratory cycles could improve arterial oxygenation was not confirmed with the CV settings we used.

Each patient studied had several criteria of severe acute respiratory failure (Table 1): low static respiratory compliance, pulmonary hypertension, increased alveolar dead space, and high alveolo-arterial difference in oxygen. Thus it can be reasonably assumed that these patients had marked reduction in lung volumes associated with large VA/Q maldistribution. It is generally believed that one of the primary therapeutic goals of any type of respiratory support is to reestablish lung volumes by increasing intrathoracic pressures. Consequently, we deliberately chose to compare the three modes of ventilation at the same level of P_{aw}. There are several reasons to suggest that the same level of P_{aw} resulted in similar increase in mean lung volume in the three modes of ventilation. First, we previously demonstrated that when HFJV is applied to patients with decreased lung compliance, the gradient between upper airway pressure and alveolar pressure is minimum (2,17,18). Second, patients with asthma or chronic obstructive pulmonary disease were excluded. Third, because P_{aw} and fluid

loading were carefully controlled and because it can be assumed that there was no gradient between upper airways and alveoli (2), the absence of change in the difference between P_{aw} and mean right atrial pressure among CPPV, HFJV, and CV for each patient strongly suggests that there was no difference in transpulmonary pressure among the three modes of ventilation (Table 2). Fourth, there were no significant differences among the three modes when considering cardiac index, stroke index, and cardiac filling pressures (Table 3). Consequently, because we applied a P_{aw} of 13.8 mm Hg (18.8 cm H₂O) to patients having a mean static respiratory compliance of 46 ml/cm H₂O, it can be assumed, according to our previous studies (2,17,18), that the resulting increase in mean lung volume above FRC was around $18.8 \times 46 = 865$ ml. In other words, we applied a high intrathoracic pressure to 13 patients with severe acute respiratory failure, resulting in a moderate increase in lung volume. This was obtained by three different methods: CPPV using a PEEP valve, HFJV using an I/E ratio of 0.43 and a driving pressure of 2.9 bars, and CV associating HFJV with a reduced driving pressure and IPPV.

When considering arterial oxygenation parameters, there were no significant differences among CPPV, HFJV, and CV. Because FI_{O₂} 1 was used during all measurements, the effects observed on PaO₂, Qs/Qt, and (A - a)DO₂ reflected only variations in true pulmonary shunt. Therefore this study cannot reply to the question as to whether HFJV alone or HFJV combined with conventional ventilation, can improve hypoxia due to low VA/Q regions, as suggested by two recent experimental studies (11,19). However, it is questionable whether this is really clinically relevant, because oxygenation deficits related to low but non-zero VA/Q regions are very sensitive to increases in FI_{O₂}. In fact, our results demonstrate that, in hypoxemic patients in acute respiratory failure, arterial oxygenation is mainly dependent on P_{aw}, whatever the mode of ventilatory support. The recent suggestion that episodic sustained inflations superimposed on high-frequency ventilation could result in marked and long-lasting improvement in arterial oxygen tension (20,21), was not supported by this study. However, end-expiratory pressure was lower during CV than

during HFJV or CPPV, mainly because P_{aw} was set at the same level during the three ventilatory modes. During CV, driving pressure of HFJV component was reduced to 1.2 bars, and the PEEP valve of the conventional ventilation component was suppressed, so that end-expiratory pressure between regular ventilatory cycles was lower than end-expiratory pressure during HFJV and CPPV. Therefore, it is possible that CV operated at an end-expiratory pressure not great enough to maintain the airways in the alveoli above their critical closing pressure allowing derecruitment to occur. One can speculate that a beneficial effect on PaO_2 could have been observed by combining IMV and PEEP—using a low frequency of 1–2 breaths/min—and HFJV—using a greater driving pressure—as suggested by a recent study (12). However, in each individual, increases in PaO_2 obtained in the three ventilatory techniques were sufficient to enable the use of FiO_2 below 0.6, and thus each technique could be considered adequate for arterial oxygenation.

When considering CO_2 elimination, CV was superior to HFJV and CPPV. Because our patients were clinically stable during the study and were heavily sedated, it can be assumed that variations in $PaCO_2$ reflected changes in CO_2 clearance rather than in CO_2 production. During CV, each individual had a lower $PaCO_2$ than during HFJV or CPPV, although identical levels of P_{aw} were applied. In other words, CO_2 elimination was improved by CV without further increasing intrathoracic pressure. This could be related to a greater minute ventilation during CV than during CPPV. However, it must be pointed out that a marked reduction in $PaCO_2$ could also have been obtained during HFJV by decreasing respiratory frequency. In a recent study (17), we demonstrated that, in patients with marked alterations in pulmonary mechanics, a decrease in respiratory frequency increases tidal volume and increases CO_2 elimination without modifying lung volume and intrathoracic pressure. Therefore, it is highly likely that an improvement in CO_2 elimination similar to the one observed during CV could have been obtained by using HFJV alone at a lower frequency, without modifying P_{aw} . It is obvious that the same result could not have been obtained by changing the ventilatory settings during CPPV.

Another interesting finding of this study concerning patients with acute respiratory failure and no circulatory shock was that we did not find any hemodynamic advantage for HFJV over CPPV or CV. Because the same level of P_{aw} was applied during each method, peak airway pressure was lower in HFJV than in CV or CPPV. Therefore our results seem to indicate that peak airway pressure does not play a predominant role in the hemodynamic repercussion of increased

intrathoracic pressure, at least in patients submitted to moderate increase in functional residual capacity. These results could also be due to the fact that neither type of ventilation had a hemodynamically significant effect, because the impairment in venous return induced by the moderate increase in functional residual capacity was easily reversed after stimulation of the aortic and carotid baroreceptors. It is possible that if a higher increase in P_{aw} and lung volume had been applied to our patients, some hemodynamic advantage would have been observed during HFJV, as suggested by a recent experimental study (22).

Finally, we were unable to find any decisive advantage for the form of CV used in this study sufficient to recommend this rather complicated and expensive type of ventilation as the primary mode of ventilatory support for patients with severe acute respiratory failure. In this study, arterial oxygenation mainly depends on P_{aw} , whatever the method of application, and CO_2 elimination can be adequately achieved by HFJV alone. Further studies using a CV with a lower IPPV rate and a higher HFJV driving pressure are required to determine whether CV maintaining minimal airway pressure above the closing pressure could improve arterial oxygenation when compared with CPPV or HFJV at the same P_{aw} . If such an advantage is demonstrated, periodic lung inflations obviously could be achieved more easily by programming "sighs" on the high frequency jet ventilator than by combining two ventilators. Another reason put forward for the use of CV is that adequate humidification can be provided via the humidifier of a conventional ventilator. Although this assumption is highly questionable, it is clear that the recent appearance of specially constructed jet humidifiers, already commercially available in Europe, enables adequate humidification and warming of the gases delivered to the patients during HFJV. In conclusion, this study does not show evidence of any real objective advantage for this form of CV associating IPPV and HFJV in adults with severe acute respiratory failure. Consequently the widespread clinical use of this technique appears to be most likely related to technical deficiencies when using HFJV, and/or the desire to make use of a "fashionable" phenomenon.

The authors thank the medical and nursing staff of the Surgical Intensive Care Unit of la Pitié Hospital for their help, Ms. G. Debradander for technical assistance, and Ms. Carole Bourassier and Ms. Corine Mataguez for typing the manuscript.

References

1. Pontoppidan H, Wilson RS, Rie MA, Schneider RC. Respiratory intensive care. *Anesthesiology* 1977;47:96–116.

Genetic Predisposition to Liver Damage after Halothane Anesthesia in Guinea Pigs

Christine A. Lunam, PhD, Michael J. Cousins, MD, FFARCS, and
Pauline de la M. Hall, FRCPA

LUNAM C, COUSINS MJ, HALL P de la M. Genetic predisposition to liver damage after halothane anesthesia in guinea pigs. *Anesth Analg* 1986;65:1143-8.

Three 4-hr normoxic (21% oxygen) exposures to 1% halothane administered 3 days apart were associated with elevations in serum alanine aminotransferase (ALT) activity in four of 20 guinea pigs after the initial and third exposures. Serum alanine aminotransferase values were not measured after the second anesthetic. Susceptibility was defined as an ALT level greater than 300 IU/L after halothane. Nonsusceptible animals, that is, animals without significant increases in ALT values after halothane, remained nonsusceptible after reexposure. Serum alanine aminotransferase values after the first and third anesthetics were significantly correlated ($r_s = 0.86$, $P < 0.001$). Two exposures of another 30 guinea pigs at a 5-week interval resulted in high elevations of ALT in the same eight animals after both anesthetics.

In contrast, after an initial exposure nonsusceptible animals remained nonsusceptible upon reexposure. Serum alanine aminotransferase levels after the first and second anesthetics were significantly correlated ($r_s = 0.85$, $P < 0.001$). The proportion of first generation (F1) males with elevated ALTs whose parents were susceptible to halothane hepatotoxicity (HH) was significantly higher than the proportion of males with elevated ALTs in a random group of 90 males ($P < 0.005$). First generation males and females of nonsusceptible parents had ALTs within the normal range after halothane exposure. These studies suggest that in the guinea pig genetic predisposition is an important determinant of susceptibility to HH, although other contributing factors are not excluded.

Key Words: GENETIC FACTORS—halothane sensitivity. ANESTHETICS, VOLATILE—halothane. LIVER—function.

We have shown that guinea pigs develop halothane hepatotoxicity without enzyme induction, hypoxia, or other conditioning factors to produce hepatic damage (1). Some guinea pigs developed severe centrilobular necrosis whereas others had no evidence of hepatic damage under identical experimental conditions. A possible explanation for this individual variation in response is that susceptibility to halothane-induced liver damage may be genetically determined. Indeed, genetic influences have been linked with hepatotoxicity of halothane in rats (2) and humans (3-5).

If an inherent susceptibility to halothane hepatotoxicity exists, then liver necrosis of similar severity

would be expected to develop in susceptible guinea pigs after each repeated exposure to halothane, provided that an adequate time interval was allowed for the liver to recover before reexposure. This study was undertaken to examine the individual response of guinea pigs to multiple halothane anesthetics. In addition, a breeding study was conducted to determine the susceptibility to halothane-induced liver damage of first generation guinea pigs whose parents had known susceptibility.

Methods

Animals

IMVS-colored (Institute of Medical and Veterinary Science, Adelaide, Australia) guinea pigs received food and tap water containing 1.0 mg/ml vitamin C ad libitum. White fluorescent light was present from 0700 to 1900 hours. 'Susceptible animals' were defined as those with susceptibility to liver damage after halothane as determined by serum alanine aminotransferase (ALT) values greater than 300 IU/L.

This study was supported in part by a Flinders University Research Grant, the National Health and Medical Research Council of Australia, and the Faculty of Anaesthetists, Royal Australasian College of Surgeons.

Received from the Department of Anatomy and Histology, School of Medicine, The Flinders University of South Australia, and the Department of Anaesthesia and Intensive Care and the Department of Pathology, Flinders Medical Centre, Bedford Park, South Australia. Accepted for publication June 2, 1986.

Address correspondence to Dr. Lunam, Department of Anatomy and Histology, School of Medicine, The Flinders University of South Australia, Bedford Park, South Australia, 5042.

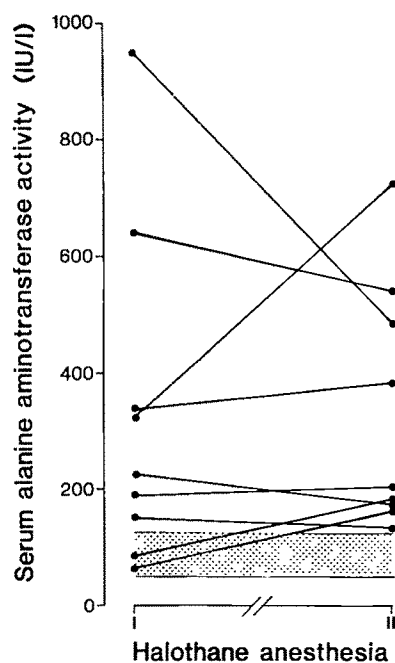


Figure 1. Three-day interval: serum alanine aminotransferase activities after multiple halothane anesthetics. I and II are 48 hr after the first and third anesthetic respectively. Shaded area is 11 animals within normal range.

Multiple Anesthetics

All anesthetics were conducted as described previously (1), that is, 1% halothane in normoxia for 4 hours. Fifty male guinea pigs weighing 500–550 g were anesthetized ten at a time in a 150 L Perspex chamber, temperature controlled at $37 \pm 1^\circ\text{C}$. A mixture of halothane and oxygen was delivered via a Fluotec MK III vaporizer at a flow rate of 6 L/min. Chamber concentrations of oxygen and carbon dioxide were monitored using a Centronix 200 MGA mass spectrometer and maintained at $21 \pm 0.5\%$ and $0.4 \pm 0.1\%$ respectively. At the end of each exposure all animals were returned to their cages and 48 hr later 1 ml of blood was drawn from each animal by cardiac puncture (under pentobarbital anesthesia, intraperitoneal 30 mg/kg) and serum ALT levels measured according to the method of Henry et al. (6).

After the initial anesthetic and blood sampling, all animals ($n = 50$) were randomly assigned into two groups. Twenty animals received a second and third exposure (1% halothane and 21% O_2 –78% N_2 for 4 hr) at intervals of 72 hr. Forty-eight hours after the third anesthesia serum ALT activity was determined. The remaining 30 guinea pigs received food and water ad libitum, and 5 weeks after the initial halothane exposure a second blood sample was taken and serum ALTs measured to confirm that ALT values had returned to within the normal range. The mean \pm SD

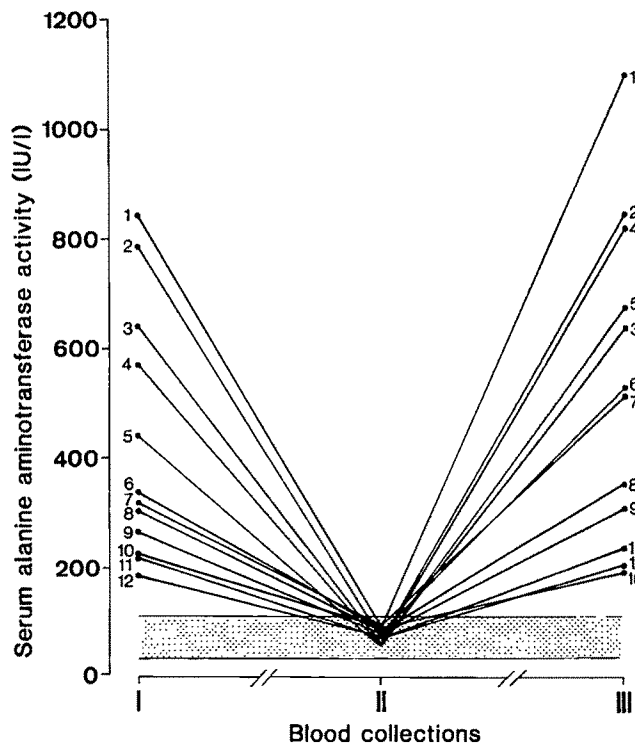


Figure 2. Five-week interval: effects of reexposure to halothane anesthesia on serum alanine aminotransferase activity. I and II are 48 hr and 35 days after the first anesthesia respectively. III is 48 hr after the second anesthetic on day 38. The shaded area represents 18 animals within normal range.

of ALT activities of 66 nonanesthetized control male guinea pigs was 60 ± 25 IU/L (7). Forty-eight hours after measurement of the second ALT the 30 guinea pigs were reexposed to halothane. Two days after reexposure, serum ALT activity was measured and compared to ALTs 48 hr after the first halothane anesthesia.

Breeding Studies

Thirty-five male IMVS-colored guinea pigs weighing 450–550 g, and 35 female IMVS-colored guinea pigs, weighing 500–700 g, were anesthetized five to ten per time, with 1% halothane in 21% oxygen for 4 hr. Forty-eight hours after exposure to halothane, all animals ($n = 70$) had blood specimens drawn by cardiac puncture for measurement of serum ALT. Four weeks later mating pairs were chosen. Guinea pigs susceptible to halothane hepatotoxicity, that is, those with ALT values greater than 300 IU/L after halothane anesthesia, were mated. Previous experiments conducted in this laboratory showed guinea pigs with ALTs greater than 300 IU/L after halothane had severe liver damage identified by light microscopy (1). Similarly nonsusceptible guinea pigs, that is, animals with ALT values

Table 1. Serum ALT Levels after Exposure to Halothane in First-Generation Guinea Pigs of Parents with ALT levels Greater Than 300 IU/L after Halothane Anesthesia

	Parents		First generation				
	♂	♀	♂	♀	♀	—	—
ALT	930	541	720	106	72	—	—
ALT	724	301	1340	356	173	—	—
ALT	463	370	♂ ^a	♀	♀	—	—
ALT	725	641	♂	—	—	—	—
ALT	654	368	♂	♂ ^a	♀	♀	♀
ALT	1300	280	732	—	160	83	92

^aDied 36 hr after halothane. Proportion of susceptible male offspring of susceptible parents significantly different from proportion in a random group of males ($P < 0.005$). ALT is alanine aminotransferase activity expressed in IU/L.

less than 125 IU/L after halothane (within normal range of non-exposed control guinea pigs), were mated. At 3 months (450–550 g), all first generation (F1) guinea pigs from both susceptible and nonsusceptible parents were exposed to 1% halothane in 21% oxygen for 4 hr and ALT levels were measured 48 hr after the halothane anesthesia.

Statistical Analysis

The association between the ALT values after repeated halothane exposures was assessed using the Spearman rank correlation coefficient. A P value less than 0.05 was accepted as statistically significant. The proportion of susceptible male offspring of parents of known susceptibility was compared to that in a random sample of 90 male guinea pigs (18 of 55 (1) plus 6 of 35 in current paper) by χ^2 -tests. The proportion of susceptible female offspring was not subjected to any statistical test, as insufficient data were available regarding the proportion of susceptible females in randomly bred animals.

Results

Multiple Halothane Anesthetics

Three-Day Intervals. A highly significant correlation was found between ALT activities after the first and third halothane anesthetics (Fig. 1) ($r_s = 0.864$, $P < 0.001$, two-tailed). Guinea pigs (4 out of 20) with high ALT values after the first halothane exposure (greater than 300 IU/L) had similar elevations in ALT after reexposure. Five animals had normal or slightly elevated ALTs after the first exposure and slight elevations after the third exposure. In contrast, 11 non-

susceptible animals, that is, those with ALT values within the range of 66 control animals (35–125 IU/L), had low or only mildly elevated ALT levels after three halothane anesthetics within 7 days.

Five-Week Interval. Serum alanine aminotransferase data after reexposure of susceptible and nonsusceptible guinea pigs to halothane-induced liver damage after a 5-week interval are reported in Figure 2. After the initial halothane anesthesia, eight of the 30 guinea pigs had ALT activities in excess of 300 IU/L. By 5 weeks after exposure to halothane the animals had recovered, as indicated by ALT values less than 125 IU/L (within normal range). After reexposure, the same 8 animals (#1–8) again developed high serum ALT levels. Four animals (#9–12) had mildly elevated ALT values at the first and second exposure. In contrast, 18 guinea pigs with ALT values within the normal range after the initial halothane anesthesia had no elevation of ALT levels after reexposure 5 weeks later. A highly significant positive correlation was found between the ALT values after each halothane anesthesia ($r_s = 0.848$, $P < 0.001$, two-tailed).

Breeding Studies

All F1 male guinea pigs bred from parents susceptible to halothane hepatotoxicity (ALT after halothane anesthesia, >300 IU/L) had highly elevated ALT values after exposure to halothane (Table 1). The proportion of susceptible male offspring of susceptible parents was significantly different from the proportion in the random group of 90 males ($P < 0.005$). Two of the F1 males died between 36 and 48 hr after halothane. Autopsies were not conducted on these animals. In contrast, F1 generation females of sus-

Table 2. Serum ALT Levels after Exposure to Halothane in First Generation Guinea Pigs of Parents with ALT Levels Less Than 125 IU/L after Halothane Anesthesia

	Parents		First generation			
	♂	♀	♂	♀	♂	♀
ALT	63	40	35	67	43	30
ALT	82	73	93	34	—	—
ALT	114	27	39	54	59	—
ALT	47	63	73	52	♀ ^a	—

^aDied before halothane anesthesia. No statistical difference was found between the proportion of nonsusceptible male offspring of nonsusceptible parents and the proportion in a random group of males ($P > 0.05$). ALT is expressed as IU/L.

ceptible parents had ALT values after halothane that were less than 300 IU/L, indicating that none of the female offspring developed severe liver damage.

Both F1 male and F1 female guinea pigs of non-susceptible parents had ALT levels after halothane anesthesia that were not elevated above control values of 125 IU/L (Table 2). The proportion of nonsusceptible male offspring was not significantly different from that of the random group of 90 males ($P > 0.05$).

Discussion

An important finding in the present study is that irrespective of either the time interval between exposures or the number of exposures to halothane, development of liver damage is reproducible in susceptible IMVS-colored guinea pigs. Conversely, guinea pigs that are not susceptible to an initial exposure to halothane show no evidence of damage at subsequent exposures. This finding is supported by the high positive correlation in serum ALTs after the first and subsequent anesthetics. These results are consistent with a genetically mediated susceptibility to halothane-induced hepatotoxicity.

Data from the breeding studies further support a genetic basis for susceptibility to halothane hepatotoxicity. One hundred percent of the first generation male guinea pigs from susceptible parents developed high serum ALT levels indicative of liver damage after a single halothane anesthesia. This figure is significantly higher than the 30% susceptibility (ALT values greater than 300 IU/L) observed in randomly selected male guinea pigs exposed to halothane in a previous study (1). On the other hand, only some F1 generation females of susceptible parents were susceptible to halothane hepatotoxicity, and to a far lesser degree

than the males, as evidenced by moderate elevations in their serum ALT levels after exposure to halothane. This finding is in contrast to a preliminary report by Lind et al. who described a similar occurrence of hepatotoxicity in both sexes of three strains of guinea pig (8). A greater susceptibility to halothane hepatotoxicity in males is also observed in phenobarbital-induced rats (9), presumably because male rats have a higher level of halothane metabolism than female rats (10). In contrast to animal studies, halothane hepatitis is more common in women than men (11). Whether such a result is due to a difference in fat content or some other difference between the sexes is not known, but obese women have high levels of reductive metabolism of halothane (12).

Evidence of a genetic basis for susceptibility to halothane hepatitis in humans has been provided by two recent studies. Human lymphocyte antigen typing of 38 patients with halothane hepatitis suggested a link between halothane hepatitis and HLA type (4). Increased susceptibility of lymphocytes to electrophilic attack was reported in 11 patients with halothane hepatitis and in ten close relatives (5). It should be pointed out that genetic susceptibility may be only incompletely expressed and that its expression may also depend upon conditional factors such as intrahepatic hypoxia. This multifactorial etiology would explain the rarity of halothane hepatitis in humans. Expression of the malignant hyperthermia trait seems to depend upon a variable degree of genetically determined susceptibility and also environmental factors (13), which explains situations where known susceptible individuals have shown no sign of malignant hyperthermia during exposure to triggering agents.

Other factors that may be important in humans include obesity, repeated halothane exposure, and immunologic response (14). The decreased latent period and increased frequency of halothane-induced

liver necrosis in patients after multiple anesthetics are consistent with an immune response. A possible mechanism for halothane hepatotoxicity is that reactive intermediates formed during halothane metabolism may covalently bind to phospholipids and proteins of the endoplasmic reticulum. According to the membrane flow hypothesis (15), these intermediates may become incorporated into the plasma membrane, form haptens, and thereby evoke an immunologic response. Current evidence points to an immunologic response involving a genetic factor in susceptible individuals (4). In the current study in the guinea pig, neither the incidence nor severity of the lesion was enhanced upon reexposure after 5 weeks. The data, therefore, do not suggest the presence of a superimposed immunologic reaction after the second anesthesia. Further studies are necessary to clarify the role of an immunologic component of halothane-induced liver damage in the guinea pig.

It is interesting to note that three successive halothane exposures to guinea pigs within 7 days neither increased nor decreased susceptibility as determined by serum ALT values. For example, guinea pigs with ALT levels less than 125 IU/L after the initial halothane anesthesia had a similar response after the third anesthesia. These results contrast with the finding in phenobarbital-treated rats that hepatic necrosis decreases with each successive anesthesia (16). Decreased halothane metabolism after the initial anesthesia, caused by impairment of the hepatic mixed function oxidase system, is a possible cause of the diminished hepatotoxicity. Importantly, residual hepatic damage and/or increased halothane metabolism in the guinea pig seem unlikely to influence the response of the liver to multiple halothane anesthetics. These results also may indicate different mechanisms of halothane hepatotoxicity in rats from those in guinea pigs, as suggested by the necessity for conditioning factors in rats (17,18) compared with the guinea pig.

These data, when considered in relation to the link between halothane metabolism and hepatotoxicity reported previously (1), are consistent with several possible coexisting determinants in the expression of halothane-induced liver necrosis. In susceptible guinea pigs, genetic variants of cytochrome P-450 may enhance minor pathways of halothane biotransformation to form extremely hepatotoxic metabolites. Such metabolites may be highly reactive, bind irreversibly to membrane-associated macromolecules, and subsequently cause disruption of hepatic membranes. A severe and critical intrahepatic hypoxia caused by halothane-induced abnormalities in control of liver blood flow, as has been reported in other species (19,20), may be superimposed on, and may even en-

hance, such a selective biotransformation of halothane in susceptible guinea pigs.

In conclusion, data from repeated halothane exposures and breeding studies strongly suggest that genetic predisposition is an important determinant of susceptibility to halothane-induced liver damage in the guinea pig. Further elucidation of the role of genetics in susceptibility to hepatotoxicity awaits a breeding study conducted through several generations.

References

1. Lynam CA, Cousins MJ, Hall P de la M. Guinea-pig model of halothane-associated hepatotoxicity in the absence of enzyme induction and hypoxia. *J Pharmacol Exp Ther* 1985;232:802-9.
2. Goulay GK, Adams JF, Cousins MJ, Hall P. Genetic differences in reductive metabolism and hepatotoxicity of halothane in three rat strains. *Anesthesiology* 1981;55:96-103.
3. Hoft RH, Bunker JP, Goodman HI, Gregory PB. Halothane hepatitis in three pairs of closely related women. *N Engl J Med* 1981;304:1023-4.
4. Oesuka S, Yamamoto M, Kasuya S, Ohtomo H, Yamamoto Y, Yoshida TO, Akaza T. HLA antigens in patients with unexplained hepatitis following halothane anesthesia. *Acta Anaesthesiol Scand* 1985;29:497-501.
5. Ferrell G, Prendergast D, Murray M. Halothane hepatitis: detection of a constitutional susceptibility factor. *N Engl J Med* 1985;313:1310-4.
6. Henry RJ, Chiamori N, Golub OJ, Berkman S. Revised spectrophotometric methods for the determination of glutamic-oxaloacetic transaminase, glutamic-pyruvic transaminase and lactic acid dehydrogenase. *Am J Clin Path* 1960;34:381-98.
7. Lynam CA. Halothane hepatotoxicity in a guinea pig model (Dissertation). Adelaide, Australia: Flinders University of South Australia, 1984, p. 108.
8. Lind RC, Gandolfi AJ, Brown BR. Halothane hepatotoxicity in both sexes of four strains of guinea pig. *Anesthesiology* 1985;63:A541.
9. Jee RC, Sipes IG, Gandolfi AJ, Brown BR Jr. Factors influencing halothane hepatotoxicity in the rat hypoxic model. *Toxicol Appl Pharmacol* 1980;52:267-77.
10. Furmer JL, Hall P de la M, Jenner MA, Cousins MJ. Sex differences in halothane metabolism and hepatotoxicity in rats. *Anesth Analg* 1985;64:563-9.
11. Zimmerman HJ. Hepatotoxicity: the adverse effects of drugs and other chemicals on the liver. New York: Appleton-Century Crofts, 1978:382-3.
12. Bentley JB, Vaughan RW, Gandolfi AJ, Cork RC. Halothane biotransformation in obese and non-obese patients. *Anesthesiology* 1982;57:94-7.
13. Cronert GA. Malignant hyperthermia. *Anesthesiology* 1980;53:395-423.
14. Cousins MJ, Plummer JL, Hall P de la M. Toxicity of volatile anesthetic agents. *Clin Anaesth* 1984;2:551-75.
15. Morre DJ, Kartenbeck J, Franke WW. Membrane flow and interconversions among endomembranes. *Biochem Biophys Acta* 1979;559:71-152.
16. Feynolds ES, Moslen MT. Liver injury following halothane anesthesia in phenobarbital-pretreated rats. *Biochem Pharmacol* 1974;23:189-95.

17. McLain GE, Sipes IG, Brown BR Jr. An animal model of halothane hepatotoxicity: roles of enzyme induction and hypoxia. *Anesthesiology* 1979;51:321-6.
18. Wood M, Berman ML, Harbison RD, Hoyle P, Phythyon JM, Wood AJJ. Halothane-induced hepatic necrosis in triiodothyronine-pretreated rats. *Anesthesiology* 1980;52:470-6.
19. Thomson IA, Fitch W, Hughes RL, Campbell D. Effect of increased concentrations of carbon dioxide during halothane anaesthesia on liver blood flow and hepatic oxygen consumption. *Br J Anaesth* 1983;55:1231-7.
20. Seyde WC, Longnecker DE. Effect of halothane, enflurane or isoflurane on the regulation of total hepatic blood flow in rats. *Anesthesiology* 1984;61:A277.

Morphine and Fentanyl Interactions with Thiopental in Relation to Movement Response to Noxious Stimulation

Igor Kissin, MD, PhD, John O. Mason III, BS, and Edwin L. Bradley Jr, PhD

KISSIN I, MASON JO III, BRADLEY EL Jr. Morphine and fentanyl interactions with thiopental in relation to movement response to noxious stimulation. 1986;65:1149-54.

The effects of morphine-thiopental and fentanyl-thiopental combinations on the movement response caused by tail clamping were studied in rats. Doses that prevented movement response when the agents were given singly and when the agents were given in combination were determined by a probit procedure and compared with isobolographic analysis. With doses of the above agents sufficient to block the

movement response to tail clamping (ED_{50} values: 4.7 (3.3-5.6) mg/kg intravenously for morphine; 8.3 (5.8-11.3) μ g/kg intravenously for fentanyl; and 18.8 (17.9-19.7) mg/kg intravenously for thiopental) both fentanyl and, to a lesser extent, morphine have a less than additive or an antagonistic interaction with thiopental. This antagonism is a relative one that does not increase the requirement for one agent upon the addition of another agent.

Key Words: ANESTHETICS, INTRAVENOUS—thiopental. ANALGESICS—morphine, fentanyl. INTERACTIONS (DRUGS).

In the last decade, opioids have become extremely popular in anesthesia. Although they can be used as sole (complete) anesthetics, most commonly they are administered in combination with conventional anesthetics, including barbiturates. Recently Eger et al. have used movement response to tail clamping in rats to determine ED_{50} values for thiopental and fentanyl (1) in a manner analogous to determining MAC values for inhaled anesthetics (2). Prevention of the movement response to noxious stimulation reflects the component of anesthetic action associated with blockade of the somatic nociceptive reflex. Barbiturates in subanesthetic doses are known to have an antianalgesic action (3-6). This antagonism between barbiturates and opioid drugs may take place only when small doses of these agents are involved, and may disappear when doses sufficient to produce anesthesia are used. On the other hand, antagonism between barbiturates and opioids in relation to the antinociceptive effect may exist even with large doses of these agents. The degree of this antagonism may not be pronounced. For example, instead of absolute antagonism (barbiturates increase the amount of an

opioid necessary to produce analgesia), only relative antagonism is present when the opioid requirement is decreased but only reduced to a degree that the conjoint effect of a barbiturate and an opioid is less than the sum of the effects of these two agents acting separately (an infraadditive effect). The aim of the present study was to define the type of interaction (supraadditive, additive, infraadditive) between morphine and fentanyl on the one hand, and thiopental on the other, with regard to purposeful movement response to noxious stimulation. The interaction was analyzed using the isobolographic method (7,8).

Methods

Experiments were performed on 168 male Sprague-Dawley rats weighing 275-325 g. The animals were stimulated for 60 sec by placement of a hemostat on the middle of the tail (pressure of 8 kg applied to a surface area of 0.25 cm²). Purposeful movement toward the clamp was considered a positive response to the stimulation. The experiments were carried out in a clear chamber 30 × 25 × 40 cm into which oxygen was delivered (4 L/min). The rat's tail (for noxious stimulation) or hind leg (for injection into the saphenous vein) could be extended to the outside of the chamber through a slot.

Each animal was given one predetermined dose of an agent or a combination of agents, and only one painful stimulation was induced. The following agents

This study was supported by research Grant 1 R01 GM 35135-01 from the National Institutes of Health.

Received from the Department of Anesthesiology, School of Medicine, University of Alabama at Birmingham, Birmingham, Alabama. Accepted for publication June 9, 1986.

Address correspondence to Dr. Kissin, Department of Anesthesiology, University of Alabama at Birmingham, University Station, Birmingham, AL 35294.

Table 1. Morphine-Thiopental Interaction as Characterized by Abolition of Purposeful Movement Response to Noxious Stimulation

Subseries	Equieffective doses of morphine–thiopental combinations				Sum of fractions	Expected sum of doses for additive interaction (fractions)	Deviation from additive interaction (expected/observed ratio)
	Morphine component		Thiopental component				
	Fraction of ED	Dose (mg/kg) ^a	Fraction of ED	Dose (mg/kg) ^a			
ED ₅₀ level							
A	0.00	0.0	1.00	18.0 (16.8,19.2)	1.00	—	—
B	0.20	0.9 (0.9,1.2)	0.95	17.8 (16.8,22.8)	1.15	1.0	0.87 ^b
C	0.64	3.0 (2.8,3.2)	0.61	11.5 (10.8,12.1)	1.25	1.0	0.80 ^c
D	0.94	4.4 (3.1,5.5)	0.21	3.9 (2.8,4.8)	1.15	1.0	0.87 ^d
E	1.00	4.7 (3.3,6.6)	0.00	0.0	1.00	—	—
ED ₉₅ level							
A	0.00	0.0	1.00	20.5 (19.3,—)	1.00	—	—
B	0.15	1.0 (0.95,3.6)	0.94	19.3 (18.3,69.7)	1.09	1.0	0.92 ^d
C	0.47	3.3 (3.1,—)	0.62	12.7 (11.8,—)	1.09	1.0	0.92 ^d
D	0.81	5.6 (4.9,31.5)	0.24	5.0 (4.3,16.2)	1.05	1.0	0.95 ^d
E	1.00	6.9 (5.5,94.0)	0.00	0.0	1.00	—	—

^a95% fiducial limits are in parenthesis.^b*P* < 0.05.^c*P* < 0.001.^dNot significant.

were used: morphine sulfate (Lilly), fentanyl citrate (Janssen), and thiopental sodium (Abbott). The agents or their combinations were injected intravenously, fentanyl and morphine in 10 sec, thiopental in 60 sec. Volume of injections was 0.5–1.0 ml. Times between injections of agents and clamping of the tail were based on the times to peak effect for these agents: 15 min for morphine, 5 min for fentanyl, and 2 min for thiopental. The animals were placed in the chamber with oxygen at least 15 min before a first injection.

Two series of experiments were performed: morphine-thiopental and fentanyl-thiopental series. In each series, the interaction between the agents was determined in two steps. First, dose-effect curves were obtained and ED₅₀ and ED₉₅ values were calculated. Then isobols were constructed to define the type of drug interaction.

Five dose-effect curves (5 subseries of experi-

ments) were determined in each series of experiments (Tables 1 and 2). Two subseries were performed with the components of a binary combination given alone (A and E subseries) and three with their various combinations (B, C, and D subseries). Four groups of four animals were used to determine the dose-effect curve for a drug or a drug combination in each subseries of experiments. On the basis of the results obtained in the experiments where agents were given alone, the relative potencies of the drugs were calculated to determine dose ratios for the combined subseries of experiments (as indicated below). In the combined subseries of experiments, the doses of both components of combinations rose from one group of rats to another by steps with the constant potency ratio between the components, which means that for each fraction of ED₅₀ of one drug, a fraction of ED₅₀ of another drug was added to maintain the same ratio between frac-

Table 2. Fentanyl-Thiopental Interaction as Characterized by Abolition of Purposeful Movement Response to Noxious Stimulation

Subseries	Equieffective doses of fentanyl–thiopental combinations					Expected sum of doses for additive interaction (fractions)	Deviation from additive interaction (expected/observed, ratio)
	Fentanyl component		Thiopental component		Sum of fractions		
	Fraction of ED	Dose (μg/kg) ^a	Fraction of ED	Dose (mg/kg) ^a			
ED ₅₀ level							
A	0.00	0.0	1.00	18.8 (17.9,19.7)	1.00	—	—
B	0.16	1.4 (1.2,1.5)	0.90	17.0 (15.3,18.7)	1.06	1.0	0.94 ^b
C	0.70	5.8 (4.6,6.4)	10.74	13.9 (10.9,15.2)	1.44	1.0	0.69 ^c
D	0.97	8.1 (7.6,8.7)	0.21	3.9 (3.6,4.2)	1.18	1.0	0.85 ^c
E	1.00	8.3 (5.8,11.3)	0.00	0.0	1.00	—	—
ED ₉₅ level							
A	0.00	0.0	1.00	20.9 (19.8,48.6)	1.00	—	—
B	0.13	1.6 (1.5,3.2)	0.94	19.8 (18.2,40.0)	1.07	1.0	0.93 ^b
C	0.57	6.7 (6.2,20.6)	0.76	15.9 (14.8,49.1)	1.33	1.00	0.75 ^c
D	0.76	9.0 (8.5,12.3)	0.21	4.3 (4.1,5.9)	0.97	1.0	1.03 ^b
E	1.00	11.8 (9.5,54.2)	0.00	0.0	1.00	—	—

^a95% fiducial limits are in parenthesis.^bNot significant.^c $P < 0.001$.^d $P < 0.05$.^e $P < 0.01$.

tions. The illustration for this may be found in the list of doses used in the experiments.

In the morphine-thiopental series of experiments, the following doses of the drugs were used. In subseries A, where thiopental was used without morphine, its doses were 18, 19, 20, and 21 mg/kg. In subseries E, where morphine was used without thiopental, its doses were 3, 4, 5, and 6 mg/kg. In subseries B, morphine and thiopental were administered in combination (15 and 2 min before the test, respectively) with the thiopental-morphine potency ratio constant at the level of 1.0:0.2 (for each fraction of ED₅₀ of thiopental a 0.2 fraction of ED₅₀ of morphine). As a result, doses of thiopental were 16, 17, 18, and 20 mg/kg, and associated doses of morphine 0.83, 0.88, 0.94, and 1.04 mg/kg. In subseries C, morphine and thiopental were administered with the potency ratio constant at the level of 1.0:1.0 with resulting

doses of 10, 11, 12, and 14 mg/kg, for thiopental and 2.5, 2.8, 3.1, and 3.6 mg/kg for morphine. In subseries D, morphine and thiopental were used with the thiopental-morphine ratio constant at the level of 0.2:1.0. As a result, doses for morphine were 3, 4, 5, and 6 mg/kg, and associated doses for thiopental were 2.6, 3.5, 4.5, and 5.2 mg/kg.

In the fentanyl-thiopental series, the following doses were used. In subseries A, where thiopental was used without fentanyl, its doses were 18, 19, 20, and 21 mg/kg. In subseries E, where fentanyl was used without thiopental, its doses were 5, 7, 10, and 13 $\mu\text{g/kg}$. In subseries B, fentanyl and thiopental were administered in combination, with the thiopental-fentanyl potency ratio constant at the level of 1.0:0.2. As a result, doses for thiopental were 15, 16, 17, 18, and 19 mg/kg, and associated doses of fentanyl were 1.20, 1.28, 1.36, 1.44, and 1.52 $\mu\text{g/kg}$. In subseries C, fen-

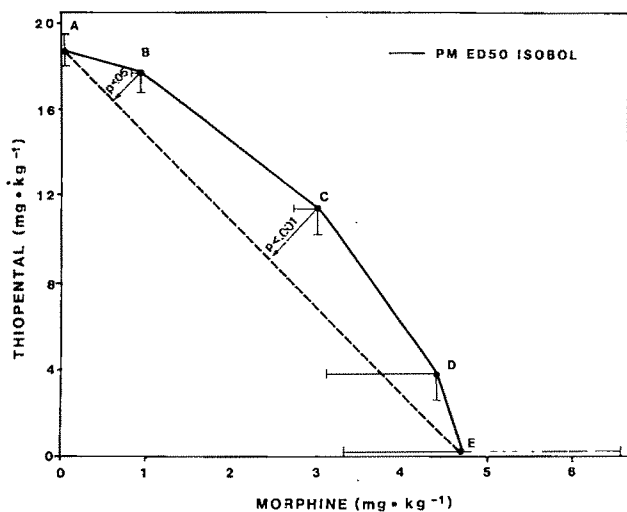


Figure 1. ED_{50} isobologram for the interaction of morphine and thiopental as characterized by abolition of purposeful movement in response to noxious stimulation. A and E are ED_{50} values for thiopental and morphine given alone (plotted on the coordinates together with 95% fiducial limits). B, C, and D are ED_{50} values for thiopental-morphine combinations. The ED_{50} isobol has been generated by connecting adjacent ED_{50} points. The dashed straight line connecting the single-drug ED_{50} points, A and E, is an additive line. P values indicate the level of statistical significance for deviations of the combined ED_{50} points from the additive line.

tanyl and thiopental were administered with the potency ratio constant at the level of 1.0:1.0 with resulting doses for thiopental, 13, 14, 15, and 16 mg/kg, and for fentanyl ($\mu\text{g/kg}$), 5.5, 5.9, 6.3, and 6.7. In subseries D, fentanyl and thiopental were used with the thiopental-fentanyl ratio constant at the level of 0.2:1.0 with resulting doses for fentanyl of 7.0, 7.5, 8.0, 8.5, and 9.0 $\mu\text{g/kg}$, and associated doses for thiopental were 3.4, 3.6, 3.8, 4.1, and 4.3 mg/kg. Determination of ED_{50} and ED_{95} values from corresponding dose-effect curves was based on the probit procedure (9).

Isobols (lines connecting equieffective doses) were determined for two levels of effect— ED_{50} and ED_{95} (7,8,10). Accordingly, ED_{50} and ED_{95} values determined from corresponding dose-effect curves were used. For example, the ED_{50} isobol for the morphine-thiopental combination (Fig. 1) connected five points: two of them were on the respective single-drug dose coordinate of the isobologram (points A and E), and three (for various combinations of morphine and thiopental, points B, C, and D) were within the dose field. The deviation of combined ED_{50} points of an isobol from an additive line (joining single-drug ED_{50} points) was measured as the length along a line passing through the origin and the point in question. This distance was used to determine if a statistically significant difference was present. The standard error

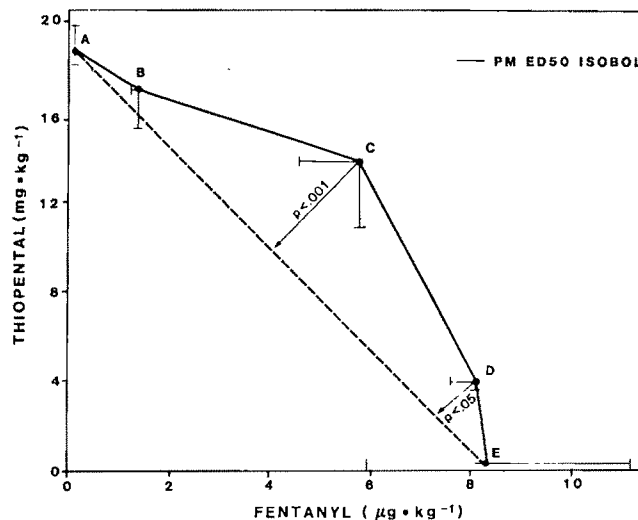


Figure 2. ED_{50} isobologram for the interaction of fentanyl and thiopental as characterized by abolition of purposeful movement caused by noxious stimulation. A and E are ED_{50} values for thiopental and fentanyl alone; B, C, and D are values for their combinations. See Figure 1 for details of construction of isobologram.

of this distance was computed by the method of propagation of error (11), and error estimates from a combined ED_{50} point, as well as single-drug ED_{50} points were used. An approximate t -test used to test the assumption of additivity was then obtained as the ratio of the measured distance to its standard error.

Animal care standards in this study were in accordance with federal and institutional policy and standards of the American Association for Accreditation of Laboratory Animal Care as specified in the *Guide for the Care and Use of Laboratory Animals* (12).

Results

The morphine-thiopental ED_{50} isobol for prevention of purposeful movement response to noxious stimulation is presented in Figure 1. The ED_{50} of thiopental was 18.8 mg/kg (95% fiducial limits, 17.9–19.7); the ED_{50} of morphine was 4.7 mg/kg (95% fiducial limits, 3.3–6.6). Each of these doses is shown on the respective single-drug dose coordinate of isobologram (points A and E). ED_{50} values for the three various combinations of morphine and thiopental are within the dose field (points B, C, and D). The isobol interconnecting adjacent ED_{50} values deviates to the right of the additive line (joining single-drug ED_{50} doses) indicating an infraadditive interaction. The deviations at points B and C were statistically significant ($P < 0.05$ and $P < 0.001$ respectively). Comparison of the observed ED_{50} and ED_{95} doses for morphine-thiopental combinations with the expected doses

for an additive interaction is presented in Table 1 in numeric form. The expected/observed ratios indicate that statistically significant deviations from additive interaction were observed at the ED₅₀ dose level; with the ED₉₅ level, only a tendency for infraadditive effect was found.

The fentanyl-thiopental ED₅₀ isobol is shown in Figure 2, and comparison of the observed ED₅₀ and ED₉₅ doses with the expected ones for an additive interaction is shown in Table 2. The fentanyl-thiopental interaction was also infraadditive. Deviations from additive interaction were statistically significant at the points C and D with the ED₅₀ dose level ($P < 0.001$ and $P < 0.05$, respectively) and at the point C with the ED₉₅ level ($P < 0.01$). The infraadditive interaction obtained in the fentanyl-thiopental series appears to be more pronounced than that in the morphine-thiopental series.

Discussion

The movement response ED₅₀ values for morphine (4.7 (3.3–6.6) mg/kg), fentanyl (8.3 (5.8–11.3) μ g/kg), and thiopental (18.8 (17.9–19.7) mg/kg) obtained in this study are close to those obtained in our previous studies (10,13,14). Interestingly, the ratio of thiopental ED₅₀ to fentanyl ED₅₀ in our present experiments was 18.8 mg/kg:0.008 mg/kg = 2265 (intravenous injection of the agents). An analogous ratio based on ED₅₀ values reported by Eger et al. (1) with subcutaneous administration of thiopental and fentanyl was 107 mg/kg:0.052 mg/kg = 2058, which is almost identical to our results.

Isobolographic analysis of our data has shown that both fentanyl and, to a lesser extent, morphine have an antagonistic (infraadditive) interaction with thiopental in relation to the prevention of purposeful movement response to noxious stimulation. This antagonism is a relative one because it does not reach the degree that requirement for one agent is increased by the addition of another agent (absolute antagonism).

Although rat experimental data and human clinical experience are difficult to correlate, the antagonism between opioids and barbiturates (used in small, subanesthetic doses) in relation to movement threshold to noxious stimulation demonstrated in rat experiments is also present in human surgical patients (3–6,15,16). The data presented by Clutton-Brock and Dundee (4,5) on the interaction between morphine and thiopental with regard to pain or movement after pressure on the anterior surface of the tibia in man demonstrate an absolute antagonism: thiopental completely abolished the effect of morphine. The impor-

tant condition for this interaction is the relatively low dose level of the interacting agents: morphine (or meperidine) was used in premedicant doses and thiopental in subanesthetic doses. Thiopental increased the threshold for motor response to the pressure on the tibia by itself only if the dose was high enough to cause unconsciousness. The effects of the combined administration of morphine and thiopental in high doses were not studied by the authors (4,5).

The antagonistic nature of the interaction between opioid drugs and barbiturates may represent absolute antagonism (increase in opioid requirement after thiopental) when small doses of agents are used, but relative antagonism (no increase in anesthetic requirement for one component of a combination) when doses of barbiturates and opioid drugs are great enough (anesthetic doses).

Rats are relatively resistant to the respiratory effect of opioids (17). We have found that morphine, 40 mg/kg, given intravenously increased P_{aCO_2} by only 30 mm Hg (9). Fentanyl in a dose of 32 μ g/kg, s.c. had no significant effect on P_{aCO_2} (18). Only when P_{aCO_2} exceeds 90 mm Hg does hypercarbia decrease anesthetic requirements (2). In our present experiments, therefore, we do not believe the influence of hypercarbia was significant. However, if such an influence were present it would diminish the observed antagonism.

No reliable data exist for speculation on the possible mechanisms for the opioid-barbiturate antagonism. Most likely it is not a pharmacologic antagonism because the sites of action of opioids (opioid receptors) are totally different from the sites of action of barbiturates (probably independent bindings sites on GABA receptor-ionophore complex) (19,20). Physiologic or functional antagonism is a more probable mechanism for the opioid-barbiturate interaction. Clutton-Brock (4) has suggested that the antianalgesic effect of barbiturates is associated with their depressive effect on some CNS inhibitory system. When high doses of barbiturates and opioid agents are used, the probability of involvement of multiple different actions for both components of the combination increases. For example, barbiturates probably should not be considered only as hypnotic agents without antinociceptive component of action. Pentobarbital used intrathecally was clearly shown to inhibit ascending activity evoked by stimulation of nociceptive afferent C fibers (21). On the other hand, a nonspecific mechanism related to lipid solubility was suggested to explain the anesthetic action of opioids (22).

In summary, interaction between morphine and fentanyl, on one side, and thiopental, on the other, in relation to purposeful movement response to nox-

ious stimulation (tail clamping) was found to be infraadditive (relative antagonism).

References

1. Shingu K, Eger EI II, Johnson BH, Lurz FW, Hickey RF. MAC values of thiopental and fentanyl in rats. *Anesth Analg* 1983;62:151-4.
2. Eger EI II. *Anesthetic uptake and action*. Baltimore: Williams and Wilkins, 1974:2.
3. Clutton-Brock J. Some pain threshold studies with particular reference to thiopentone. *Anaesthesia* 1960;15:71-2.
4. Clutton-Brock J. Pain and the barbiturates. *Anaesthesia* 1961;16:80-8.
5. Dundee W. Alterations in response to somatic pain associated with anaesthesia. II: The effect of thiopentone and pentobarbitone. *Br J Anaesth* 1960;32:407-14.
6. Dundee W, Moore J. Alterations in response to somatic pain associated with anaesthesia. I: An evaluation of a method of analgesimetry. *Br J Anaesth* 1960;32:396-406.
7. Loewe S, Muischnek H. Ueber Kombinationswirkungen. I. Mitteilung: Hilfsmittel der Fragestellung. *Naunyn Schmiedeberg's Arch Pharmacol* 1926;114:313-26.
8. Loewe S, Aldous RA, Fox SR, Johnson DG, Perkins W. Isobols of dose-effect relations in the combination of trimethadione and pentylenetetrazole. *J Pharmacol Exp Ther* 1955;113:475-80.
9. Finney DJ. *Probit analysis*. London: Cambridge University Press, 1952.
10. Kissin I, Kerr CR, Smith LR. Morphine-halothane interaction in rats. *Anesthesiology* 1984;60:553-61.
11. Ku HH. Notes on the use of propagation of error formulas. *J Res Natl Bureau Stand* 1966;70:263-73.
12. Department of Health, Education, and Welfare. *Guide for the care and use of laboratory animals*. Washington: U.S. Government Printing Office, 1978; DHEW Publication no. (NIH) 78-23.
13. Kissin I, McGee T, Smith LR. The indices of potency for intravenous anesthetics. *Can Anaesth Soc J* 1981;28:585-90.
14. Kissin I, Brown PT. Reserpine-induced changes in anesthetic action of fentanyl. *Anesthesiology* 1985;62:597-600.
15. Neal MJ. The hyperalgesic action of barbiturates in mice. *Br J Pharmacol* 1965;24:170-7.
16. Kissin I, Brown PT, Green D. Thiopental-fentanyl antinociceptive interaction in rats. *Anesthesiology* 1985;63:A201.
17. Isom GE, Nelson RB, Edlin AI. A comparison of the lethal and respiratory effects of morphine in Long-Evans and Sprague-Dawley rats. *Arch Int Pharmacodyn* 1969;182:130-8.
18. Shingu K, Eger EI II, Johnson BH, Lurz FW, Taber V. Effects of halothane, isoflurane, enflurane, thiopental, and fentanyl on blood gas values in rats exposed to hypoxia. *Anesth Analg* 1983;62:155-9.
19. Leeb-Lundberg F, Olsen RW. Interactions of barbiturates of various pharmacological categories with benzodiazepine receptors. *Mol Pharmacol* 1982;21:320-8.
20. Segal M, Barker JL. Rat hippocampal neurons in culture: voltage-clamp analysis of inhibitory synaptic connections. *J Neurophysiol* 1984;52:469-87.
21. Bernatzky G, Doi T, Jurnal I. Effects of intrathecally administered pentobarbital and naloxone on the activity evoked in ascending axons of the rat spinal cord by stimulation of afferent A and C fibres: further evidence for tonic endorphinergic inhibition in nociception. *Naunyn Schmiedeberg's Arch Pharmacol* 1983;323:211-6.
22. Dodson BA, Miller KW. Evidence for a dual mechanism in the anesthetic action of an opiate peptide. *Anesthesiology*, 1983; 59:A31.

Pharmacokinetics and Placental Transfer of Intravenous and Epidural Alfentanil in Parturient Women

E. Gepts, MD, L. Heytens, MD, and F. Camu, MD

GEPTS E, HEYTENS L, CAMU F. Pharmacokinetics and placental transfer of intravenous and epidural alfentanil in parturient women. *Anesth Analg* 1986;65:1155-60.

Alfentanil was administered as a 30 $\mu\text{g/kg}$ single intravenous injection to five healthy women scheduled for elective cesarean section (group A). In five pregnant women normal vaginal delivery was supported by epidural analgesia with a 30 $\mu\text{g/kg}$ loading dose followed by a 30 $\mu\text{g/kg}^{-1}\text{hr}^{-1}$ infusion of alfentanil (group B). Five healthy nonpregnant women scheduled for minor general surgery received 120 $\mu\text{g/kg}$ alfentanil intravenously as a bolus before surgical incision (group C). In groups A and B plasma alfentanil concentrations, alfentanil plasma protein binding, and α_1 -acid glycoprotein (α_1 -AGP) concentrations were measured in maternal and umbilical arterial or venous blood samples at delivery. Multiple arterial sampling in groups A and C for measurement of alfentanil plasma concentration decay analysis indicated three-compartmental characteristics in most patients. In the pregnant population terminal half-life ($t_{1/2\beta}$), volume of distribution at steady state (V_{dss}), and total plasma clearance (Cl_p) amounted to 103 ± 67 min, 541 ± 155 ml/kg and 6.48 ± 0.85 ml/kg $^{-1}\text{min}^{-1}$, respectively (mean \pm SD), and did not differ significantly in nonpregnant patients. In groups A and B the fetal-maternal ratios indicated a concentration gradient for the total plasma alfentanil content (ratio of total alfentanil concentrations in umbilical venous and maternal blood (U_v/M), 0.31 ± 0.08 and 0.28 ± 0.06 (mean \pm SD) in groups A and B respectively) with a larger protein binding capacity in maternal plasma (group A, $85 \pm 3\%$; group B, $90 \pm 1\%$) (mean \pm SD). The concentration of α_1 -AGP, the most important binding protein for alfentanil, was significantly lower in umbilical venous blood (22 ± 7 mg/100 ml) (mean \pm SD) than in the maternal samples (group A, 42 ± 5 mg/100 ml; group B, 55 ± 13 mg/100 ml) (mean \pm SD). A positive correlation was observed between the plasma alfentanil concentrations of total alfentanil and free alfentanil in the mothers and neonates, as well as between the α_1 -AGP concentration and the bound to free alfentanil fraction (f_b/f_u). Thus the intravenous pharmacokinetics of a bolus dose of alfentanil are not significantly altered in late pregnancy. Free alfentanil easily crossed the placental barrier. Because of decreased fetal α_1 -AGP levels, a larger free alfentanil fraction existed in neonates.

tan l content (ratio of total alfentanil concentrations in umbilical venous and maternal blood (U_v/M), 0.31 ± 0.08 and 0.28 ± 0.06 (mean \pm SD) in groups A and B respectively) with a larger protein binding capacity in maternal plasma (group A, $85 \pm 3\%$; group B, $90 \pm 1\%$) (mean \pm SD). The concentration of α_1 -AGP, the most important binding protein for alfentanil, was significantly lower in umbilical venous blood (22 ± 7 mg/100 ml) (mean \pm SD) than in the maternal samples (group A, 42 ± 5 mg/100 ml; group B, 55 ± 13 mg/100 ml) (mean \pm SD). A positive correlation was observed between the plasma alfentanil concentrations of total alfentanil and free alfentanil in the mothers and neonates, as well as between the α_1 -AGP concentration and the bound to free alfentanil fraction (f_b/f_u). Thus the intravenous pharmacokinetics of a bolus dose of alfentanil are not significantly altered in late pregnancy. Free alfentanil easily crossed the placental barrier. Because of decreased fetal α_1 -AGP levels, a larger free alfentanil fraction existed in neonates.

Key Words: ANALGESICS—alfentanil. ANESTHESIA, OBSTETRIC. PHARMACOKINETICS—alfentanil.

General anesthesia for cesarean section must provide adequate fetal oxygenation while avoiding maternal awareness and deleterious effects to the fetus and newborn. The light levels of anesthesia obtained at induction often result in a high incidence of awareness, usually evinced by insufficient pain control. In turn, lack of analgesia may induce maternal and fetal side effects because of uterine vasoconstriction.

Alfentanil is a potent, short-acting, lipophilic opioid

agonist analgesic with a slight hypnotic activity. Its physicochemical properties result in a relatively small volume of distribution yielding a short elimination half-life despite a hepatic clearance of only one-third the hepatic blood flow (1-3). The plasma protein binding of the drug is extensive and involves mainly α_1 -acid glycoprotein (α_1 -AGP), less albumin and a little α -globulin (4). The appropriate use of alfentanil in obstetrical anesthesia might provide a means for adequate control of surgical pain and complete amnesia to parurients. Its short duration of action might reduce the incidence of respiratory depression in neonates despite its probable placental transfer. However, exposure of the fetus to drugs given to the mother is not just governed by the pharmacokinetic properties of the drug; it is also affected by protein binding (5). The binding of drugs to maternal and fetal plasma proteins is influenced by the changes in serum al-

Supported by the National Foundation for Medical Research (F.G.W.O. Grant No. 3006585), and presented in part at the Joint Meeting of the Belgian, Dutch, and German Pharmacological and Toxicological Societies (September 1985).

Received from the Department of Anesthesiology, Flemish Free University of Brussels, Brussels, Belgium. Accepted for publication June 10, 1986.

Address correspondence to Dr. Camu, Department of Anesthesia, Academisch Ziekenhuis V.U.B., Laarbeeklaan 101, B-1090 Brussels, Belgium.

bumin, α_1 -AGP, fatty acids, and lipoproteins observed during pregnancy (6-8).

The aim of this study was to evaluate the pharmacokinetic behaviour of alfentanil in pregnant women. A comparison of these values was made with those found in nonpregnant patients. The effects of plasma protein binding on the placental transfer of alfentanil were also investigated.

Methods

Approval of the study protocol was obtained from the University Committee of Human Research. Informed consent was given by all patients participating in the study. The study included 15 patients divided into three groups: five healthy women at term scheduled for elective cesarean section (group A), five healthy women at term given epidural analgesia with alfentanil for vaginal delivery (group B), and five healthy nonpregnant women scheduled for minor general surgery (group C).

Different anesthetic procedures were followed for the different groups. Patients in group A had an indwelling intravenous catheter (for drug injection) and a radial artery catheter (for blood sampling) inserted while under local anesthesia. The patients were preoxygenated and anesthesia was induced with thiopental, 3 mg/kg intravenously, and with succinylcholine, 1 mg/kg intravenously, to facilitate tracheal intubation while cricoid pressure was applied. Vecuronium, 0.04 mg/kg, and alfentanil, 30 μ g/kg, were injected intravenously thereafter. Delivery was expected within 10 min after alfentanil injection. Before delivery, anesthesia was maintained with nitrous oxide in oxygen (1:1), whereas after delivery isoflurane (1 MAC) was added to the nitrous oxide-oxygen mixture (2:1). Normocapnia was produced with mechanical ventilation. Throughout the procedure a left-side lateral tilt was ensured to avoid aortocaval compression by the gravid uterus. Heparinized arterial blood samples were taken before and 2, 4, 6, 8, 10, 15, 30, 60, 90, 120, 150, 180, 240, and 300 min after the alfentanil bolus injection. Umbilical venous and arterial blood samples were taken at delivery simultaneously with a maternal arterial sample. All samples were immediately centrifuged, and the plasma samples were stored at -20°C until analyzed.

In patients in group B, an epidural catheter (20 gauge) was placed at the T 11-12 level at the very start of labor. After an epidural bolus injection of alfentanil, 30 μ g/kg, a continuous infusion of alfentanil, 30 μ g \cdot kg $^{-1}\cdot$ hr $^{-1}$, was administered epidurally until delivery. Bupivacaine, 0.25%, was given if the anal-

gesia provided by alfentanil alone became inadequate. Maternal venous blood samples and arterial and venous blood samples from the umbilical cord were taken at birth for assay of alfentanil.

Patients in group C were premedicated with oral diazepam, 10 mg, and intramuscular atropine, 0.25 mg, 1 hr before surgery. Anesthesia was induced with etomidate, 0.2 mg/kg, and with succinylcholine, 1 mg/kg, to facilitate tracheal intubation. Anesthesia was maintained with halothane, 0.6-1 vol%, in a mixture of nitrous oxide-oxygen (2:1) according to clinical needs. Normocapnic ventilation was provided by controlled ventilation. Prior to surgical incision, alfentanil, 120 μ g/kg, was injected as a bolus intravenously. Heparinized arterial blood samples were taken before and at 2, 5, 10, 15, 30, 45, 60, 90, and 120 min after drug administration, and then hourly for 6 hr after drug administration. Plasma was separated by centrifugation and stored frozen until analysis.

Total plasma alfentanil concentration was assayed by radioimmunoassay (limit of sensitivity, 1 ng/ml) (9). Alfentanil plasma protein binding was measured in vitro by equilibrium dialysis of the samples spiked with specifically tritium-labelled alfentanil followed by liquid scintillation spectrometry (4). Alfentanil- ^3H hydrochloride (Janssen Life Sciences Products, Beerse, Belgium) had a specific activity of 16.3 Ci/mmol and a radioclinical purity of 99.8% (radio-HPLC). Equilibrium dialysis was carried out in a Dianorm apparatus at 37°C against isotonic Sorensen 0.067 M phosphate buffer, pH 7.17, resulting in a final pH of 7.40 ± 0.03 after 4 hr of dialysis. Levels of α_1 -AGP were determined by radial immunodiffusion using NOR-Partigen α_1 -AGP plates (Behringwerke, Marburg, FRG). The levels of free alfentanil were calculated from the concentration of total alfentanil times the free fraction, i.e., $100 - \text{percent bound to plasma proteins}$. Blood gas analysis was performed on the umbilical venous and maternal arterial blood sample at delivery.

The individual concentration-time data (C_t) were fitted to a multicompartmental open mamillary model using a nonlinear extended least squares regression analysis with variances proportional to some power of the predicted value of the dependent variable (10). Elimination was assumed to occur from the central compartment with first-order kinetics. Statistical testing was based on the smallest ($-$) log likelihood, and Schwarz and Leonard criteria determined the appropriate model. Derived pharmacokinetic parameters including apparent volume of distribution ($V_{d\beta}$), volume of distribution at steady state (V_{dss}), volume of the central compartment (V_c), terminal half-life ($t_{1/2\beta}$), total plasma clearance (Cl_p) and the microconstant for drug elimination (k_{10}) were calculated (11). The frac-

Table 1. Patient Characteristics

	Group A	Group B	Group C
Population	At term	At term	Nonpregnant
Number of patients	5	5	5
Age ^a (yr)	30.2 ± 2.6	24.4 ± 5.8	43.0 ± 9.0
Weight ^a (kg)	64.2 ± 6.1	70.6 ± 6.1	57.6 ± 9.7
Alfentanil dose	30 μg/kg	20 μg/kg + 30 μg/kg/hr	120 μg/kg
Route of administration	Intravenous bolus	Epidural bolus + infusion	Intravenous bolus
Procedure	Cesarean section	Spontaneous delivery with epidural analgesia	Thyroidectomy
Hematocrit ^a (percent)	34.2 ± 4.7	34.6 ± 1.7	42.5 ± 1.8
Maternal pH ^a	7.32 ± 0.04	7.37 ± 0.01	—
Neonatal pH ^a	7.29 ± 0.01	7.30 ± 0.07	—

^aValues are mean ± SD.

tion of dose eliminated during the terminal phase was calculated as the ratio B/β (terminal macroconstant/terminal microconstant) to the total area under the concentration-time curve: $(B/\beta)/AUC$. Noncompartmental analysis based on the statistical moments theory was performed using the log trapezoidal rule. Mean residence time (MRT), $V_{d_{ss}}$, and clearance were derived from the area under the concentration vs time plots to infinity (AUC) and the area under the $C_t \times t$ vs time plot to infinity (AUMC) (12).

Results

The physical characteristics of the patients are listed in Table 1. By means of analysis of variance, a significant difference was found between the ages of the three groups; the nonpregnant patients tended to be older.

Pharmacokinetics

Curve fitting of the individual concentration-time data indicated that a three-compartment open mamillary model, with elimination occurring from the central compartment only, was most appropriate in three of the pregnant patients and in four of the nonpregnant group. The data of the remaining patients in each group fitted best to a biexponential equation. The derived pharmacokinetic parameters were calculated for each subject individually according to the most appropriate model. The mean values of the pharmacokinetic parameters are summarized in Table 2. No meaningful differences were observed between the pregnant and nonpregnant patients. Values derived by noncompartmental analysis for apparent volume of distribution at steady state and clearance were very similar to those values found by the multicompartmental approach, thus validating both methods for estimation of these parameters. The volumes V_c and

$V_{d_{ss}}$ approximated the extracellular water and the total body water volumes, respectively, probably in relation to the high degree of protein binding of alfentanil. The MRT (time required to eliminate 63.2% of the given intravenous bolus dose) and $t_{1/2\beta}$ closely agreed in both groups. The plasma clearance indicated a hepatic extraction ratio of 0.39 ± 0.04 in group A and 0.39 ± 0.13 in group C (mean ± SD). The fraction of alfentanil eliminated during the terminal phase was $59.8 \pm 18.1\%$, indicating that an important amount of the drug was already eliminated while distribution completed. Thus terminal half-life did not seem representative of elimination half-life.

Placental Transfer (Table 3)

The mean fetal to maternal ratio of total alfentanil plasma concentrations was 0.29 in both groups A and B taken together. Protein binding capacity for alfentanil was significantly greater in mothers than in neonates ($P < 0.001$), resulting in fairly equal levels of free (unbound) alfentanil (f_u) (calculated as total level times fraction unbound) in both mother (M) and neonate (F) (F/M ratio 0.97 ± 0.43) (mean ± SD), thus indicating easy placental transfer of the free drug. Positive correlations were observed between the plasma concentrations of total alfentanil ($r = 0.919$, $P < 0.001$) and free alfentanil ($r = 0.959$, $P < 0.001$) in the mothers and neonates.

Both the fraction of bound drug (f_b) in plasma and the ratio of bound to free alfentanil were significantly greater in maternal than in fetal blood ($P < 0.001$). If a weak relation existed between the maternal f_b/f_u ratio and maternal total plasma alfentanil concentrations ($r = 0.634$, $P < 0.05$), no level dependence was seen for maternal or fetal alfentanil binding and plasma concentrations of the drug. Because alfentanil binds extensively to α_1 -AGP, to a great extent the differences in protein binding generating the free alfentanil

Table 2. Pharmacokinetics of Alfentanil in Pregnant and Nonpregnant Patients

Parameters ^a	Group A (pregnant)	Group C (nonpregnant)
Multicompartmental analysis		
$t_{1/2\beta}$ (min)	102.8 \pm 66.6	103.5 \pm 49.7
V_c (L)	8.696 \pm 2.782	9.650 \pm 2.107
V_c (L/kg)	0.134 \pm 0.036	0.169 \pm 0.025
Vd_{β} (L)	61.948 \pm 39.668	51.432 \pm 19.788
Vd_{β} (L/kg)	0.953 \pm 0.583	0.891 \pm 0.340
Vd_{ss} (L)	34.923 \pm 11.293	31.670 \pm 10.125
Vd_{ss} (L/kg)	0.541 \pm 0.155	0.543 \pm 0.121
Cl_p (ml \cdot kg ⁻¹ \cdot min ⁻¹)	6.481 \pm 0.853	6.584 \pm 2.302
k_{10} (min ⁻¹)	0.0501 \pm 0.0098	0.0393 \pm 0.0146
Noncompartmental analysis		
MRT (min)	91.5 \pm 28.1	103.2 \pm 66.5
Vd_{ss} (L)	40.928 \pm 12.973	35.520 \pm 11.207
Vd_{ss} (L/kg)	0.635 \pm 0.181	0.611 \pm 0.148
Cl_p (ml \cdot kg ⁻¹ \cdot min ⁻¹)	6.993 \pm 0.872	7.089 \pm 2.546

All values are mean \pm SD.^aSee text for abbreviations.

levels could be accounted for by the lower levels of this plasma component in neonates (F/M ratio, 0.45 ± 0.15) (mean \pm SD). Indeed, a positive correlation was observed between the α_1 -AGP concentrations and the f_b/f_u ratio ($r = 0.896$, $P < 0.001$).

The pH values of umbilical venous and maternal arterial blood were not greatly different (Table 1) and thus were unlikely to contribute to the maternal-fetal plasma alfentanil binding differences.

Discussion

Many of the anatomic and physiological transformations associated with pregnancy and childbirth influence the pharmacokinetic behaviour of drugs. Factors important in determining the extent of fetal exposure to a maternally administered drug are the changes in plasma protein concentrations and acid-base equilibrium, the increase in plasma volume and cardiac output, and the sixfold increase in peripheral blood flow and tissue perfusion (13). Together with the physicochemical properties of the drug, these factors govern how readily the drug is distributed into fetal and maternal tissues. In nonpregnant patients two- and three-compartmental models have been proposed for determining the pharmacokinetic profile of alfentanil (1-3). In the present study, the data from pregnant subjects were best fitted with a triexponential equation (three patients out of five), whereas a biexponential equation was more appropriate for two pregnant patients and one nonpregnant patient. These models assumed first-order distribution, transfer, and

elimination processes. In the pregnant population a further assumption was made that clearances between mother and fetus were equal in both directions.

Basic lipophilic compounds such as alfentanil are considered able to cross all cell membranes rapidly, including the blood-brain barrier and the placental barrier. The fetoplacental unit has to be considered a vessel-rich, highly perfused tissue; in late pregnancy the placental circulation may account for as much as 15% of the increased maternal cardiac output (14). Because of this high uterine blood flow, the fetal compartment is usually included in the central maternal compartment. A larger volume of distribution thus could be expected. In the present study, no significant changes in the volumes of distribution appeared with pregnancy. The inability to demonstrate significant distribution volume changes may also have resulted from the absence of large differences in body weight between patients in group A and group C.

Another important factor in determining the extent of drug distribution is plasma protein binding, which in turn also conditions the intensity and duration of action of drugs. Plasma protein concentrations vary with pregnancy. Serum albumin concentrations decrease significantly, lipoproteins and fatty acids increase, and α_1 -AGP plasma concentrations remain unaffected (6-8). Alfentanil is highly bound mainly to α_1 -AGP, much less to albumin, and only a little to α -globulin (4). As a result, no important alterations in alfentanil plasma protein binding capacity were expected during pregnancy. Indeed, the fraction of alfentanil bound in plasma in the pregnant subjects amounted to 81-92%, which is clearly not signifi-

Table 3. Placental Transfer and Plasma Binding of Alfentanil

Group	Patient number	Plasma concentration (ng/ml)			Protein binding							
		Maternal (M)	Umbilical venous (U _v)	Umbilical arterial (U _a)	U _v /M ^a	U _a /U _v	Mother		Child			
							f _b ^b	f _b /f _a ^c	α ₁ AGP _d	f _b ^b	f _b /f _a ^c	α ₁ AGP ^d
Group A	1	78.4	32.4	—	0.41	—	81.13	4.31	43.3	74.18	2.87	30.1
	2	118.0	33.6	18.1	0.28	0.54	87.00	6.69	46.8	63.44	1.74	15.1
	3	61.5	17.9	—	0.29	—	—	—	—	—	—	—
	4	70.0	25.0	—	0.36	—	87.50	7.00	36.6	76.37	3.23	20.9
	5	67.8	13.9	12.9	0.21	0.93	—	—	—	—	—	—
Mean ± SD		79.1 ± 22.5	24.6 ± 8.7	—	0.31 ± 0.08	—	85.21 ± 3.54	6.00 ± 1.47	42.23 ± 5.18	71.33 ± 6.93	2.61 ± 0.78	22.03 ± 7.56
Group B	1	29.4	6.4	8.07	0.22	1.26	90.00	9.00	39.9	64.03	1.78	18.0
	2	21.5	4.8	4.11	0.22	0.87	88.35	7.58	46.8	60.65	1.54	20.9
	3	39.1	12.8	—	0.33	—	89.99	8.99	54.0	70.74	2.42	20.9
	4	47.7	16.2	—	0.34	—	89.42	8.45	61.5	58.39	1.40	33.3
	5	27.3	7.4	—	0.27	—	92.31	12.00	73.3	69.61	2.30	15.1
Mean ± SD		33.0 ± 10.4	9.5 ± 4.8	—	0.28 ± 0.06	—	90.01 ± 1.45	9.20 ± 1.67	55.10 ± 12.97	64.68 ± 5.41	1.89 ± 0.45	21.64 ± 6.95

^aRatio of total alfentanil concentrations in umbilical venous to maternal blood.^bFraction of bound drug in plasma expressed as percent.^cRatio of bound to free alfentanil in plasma.^dLevels of α_1 -acid glycoprotein (mg/100 ml).

cantly different from previously reported data from nonpregnant subjects (4,15).

The plasma clearance and the hepatic extraction ratio of alfentanil appeared to be unchanged in our pregnant patients. Associated with normal values of protein binding and liver flow, the intrinsic clearance for alfentanil was probably unaffected by the hormonal changes of pregnancy. The interrelationships between volume of distribution, clearance, elimination rate constant ($Cl = V_c \times k_{10}$), and terminal half-life indicate the latter two parameters will also remain similar for pregnant and nonpregnant patients, as demonstrated in Table 2. Thus pharmacokinetic linearity was preserved between fourfold bolus doses (30 $\mu\text{g/kg}$ in pregnant and 120 $\mu\text{g/kg}$ in nonpregnant patients).

Because of its lipid solubility, free (unbound) alfentanil is expected to cross the placental barrier. Differences in protein bound drug fraction might explain the U_v/M gradient for total alfentanil plasma levels (0.30). Indeed, the fetal alfentanil plasma protein binding capacity was 76% of the maternal value. This finding could be due to the reduced affinity of fetal albumin for drugs (16). But most importantly, the main alfentanil binding protein α_1 -AGP showed fetal plasma concentrations amounting to 43% of the maternal which correlates with previously reported values (7,8). The observed differences in pH between maternal and fetal blood were too small to have a significant influence on the placental transfer of alfentanil. The fraction of alfentanil bound to plasma proteins remains fairly constant within physiological boundaries of blood pH (4).

The low U_v/M ratio observed was not related to the dosing-delivery interval. In group A, a delay in equilibrium between maternal and fetal blood could hypothetically exist because of non-steady state conditions during drug distribution. On the other hand, in group B the fetal samples obtained were more representative of a steady state situation as the maternal epidural infusions of alfentanil lasted on average 4 hr before delivery. The transfer of alfentanil across the placenta was assumed to be complete at time of sampling. Nevertheless, the U_v/M ratios were identical in both groups of patients. This finding also supports the concept that transplacental passage of alfentanil is very rapid and confirmed the validity of including the fetal compartment in the central maternal compartment of the pharmacokinetic model.

We conclude that the pharmacokinetic behaviour of alfentanil given as a single intravenous bolus dose in late pregnancy is not significantly different than in nonpregnant females. The important reduction of fetal α_1 -AGP levels allowed large unbound plasma al-

fentanyl fractions. Thus similar pharmacologic effects are to be expected in neonates and mothers as the free drug concentrations are comparable in both.

This study was supported by the Belgian Foundation for Medical Research (Grant No. 3006585). The authors wish to thank R. Woestenborghs (Department of Drug Metabolism and Pharmacokinetics, Janssen Pharmaceutica, Beerse) for the analysis of blood samples. In addition, the authors are indebted to Professor J. J. Amy (head, Department of Gynecology and Obstetrics), for his support of this project and to Miss I. Rasschaert for her secretarial assistance.

References

1. Bovill JG, Sebel PS. Pharmacokinetics of alfentanil (R 39209): a new opioid analgesic. *Anesthesiology* 1982;57:439-43.
2. Camu F, Gepts E, Rucquoi M, Heykants J. Pharmacokinetics of alfentanil in man. *Anesth Analg* 1982;61:657-61.
3. Schuttler J, Stoeckel H. Alfentanil (R 39209): ein neues kurz-wirkendes Opioid. *Anaesthesist* 1982;31:10-4.
4. Meuldermans WEG, Hurkmans RMA, Heykants JJP. Plasma protein binding and distribution of fentanyl, sufentanil, alfentanil and lofentanil in blood. *Arch Int Pharmacol Ther* 1982;257:4-19.
5. Green TP, O'Dea RF, Mirkin BL. Determinants of drug disposition and effect in the fetus. *Ann Rev Pharmacol Toxicol* 1979;19:285-322.
6. Dean M, Stock B, Patterson RJ, Levy G. Serum protein binding of drugs during and after pregnancy in humans. *Clin Pharmacol Ther* 1980;28:253-61.
7. Nation RL. Meperidine binding in maternal and fetal plasma. *Clin Pharmacol Ther* 1981;29:472-9.
8. Wood M, Wood AJJ. Changes in plasma drug binding and α_1 -acid glycoprotein in mother and newborn infant. *Clin Pharmacol Ther* 1981;29:522-6.
9. Michiels M, Hendriks R, Heykants J. Radioimmunoassay of the new opiate analgesics alfentanil and sufentanil. Pharmacokinetic profile in man. *J Pharmacol* 1983;35:86-93.
10. Peck CC, Beal SL, Sheiner LB, Nichols AI. Extended least squares nonlinear regression: a possible solution to the "choice of weights" problem in analysis of individual pharmacokinetic data. *J Pharmacokin Biopharm* 1984;12:545-58.
11. Gibaldi M, Perrier D. *Pharmacokinetics*. 2nd ed. New York: Marcel Dekker, 1982:84-111.
12. Riegelman S, Collier P. The application of statistical moments theory to the evaluation of in vivo dissolution time and absorption time. *J Pharmacokin Biopharm* 1980;8:509-34.
13. Katz M, Sahal MM. Skin perfusion in pregnancy. *Am J Obstet Gynecol* 1980;137:30-3.
14. Dilts PV, Brinkman CR, Kirschbaum TH, Assali NS. Uterine and systemic hemodynamic interrelationships and their response to hypoxia. *Am J Obstet Gynecol* 1969;103:138-43.
15. Bower S, Hull CJ. Comparative pharmacokinetics of fentanyl and alfentanil. *Br J Anaesth* 1982;54:871-7.
16. Wallace S. Factors affecting drug-protein binding in the plasma of newborn infants. *Br J Clin Pharmacol* 1976;3:510-2.

Constant Flow Ventilation in Anesthetized Patients: Efficacy and Safety

Peter H. Breen, MD, J. Iasha Sznajder, MD, Paulette Morrison, RRT, Don Hatch,
Larry D. H. Wood, MD, and Douglas B. Craig, MD

BREEN PH, SZNAJDER JI, MORRISON P, HATCH D, WOOD LDH, CRAIG DB. Constant flow ventilation in anesthetized patients: efficacy and safety. *Anesth Analg* 1986;65:1161-9

Constant flow ventilation (CFV) maintains normal gas exchange in apneic dogs and has potential clinical application during thoracic surgery or pulmonary edema. We compared CFV and intermittent positive pressure ventilation (IPPV) in five healthy, anesthetized, fentanyl, diazepam, and nitrous oxide) and paralyzed patients undergoing nonthoracic operations. Constant flow ventilation was delivered at a total flow of $0.9\text{--}1.6\text{ L}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$ (nitrous oxide-oxygen at 1:1) into two tubes of 2.5–3.5 mm inner diameter attached to each side of an 8–9 mm inner diameter orotracheal tube (OTT). Under bronchoscopic guidance, the CFV-OTT

was advanced to position each ventilating tube at a mainstem bronchial orifice. Gas exhausted through the OTT lumen. If intrathoracic pressure exceeded a preset limit, a solenoid valve automatically interrupted gas flow to the patient to prevent barotrauma. Compared to IPPV, during CFV for up to 30 min average PaCO_2 increased to 69.2 ± 14.5 from 35.3 ± 2.9 mm Hg, reflecting a calculated alveolar ventilation (\dot{V}_A) of $46 \pm 22\%$ of the eupneic level. We suggest that a technique combining CFV at lower flow rates with IPPV may prove clinically useful by allowing decreased tidal volume and inspiratory pressure while maintaining normal \dot{V}_A .

Key Words: VENTILATION—constant flow.

Constant flow ventilation (CFV) uses very high gas flows (total $\approx 1\text{ L}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$) to maintain normal gas exchange in apneic animals (1–4), two small orotracheal catheters delivering gas flows into each mainstem bronchus with gas exiting through the open airway. Like apneic diffusion oxygenation (ADO, oxygen flow across the proximal opening of a patent airway) (5), CFV results in good oxygenation. However, CFV also maintains normal CO_2 elimination in animals, in sharp contrast to ADO during which no CO_2 removal occurs (5,6).

If CFV could also maintain CO_2 elimination in patients, then some problems occurring during conventional intermittent positive pressure ventilation (IPPV) could be reduced. During bronchoscopy or during large airway and intrathoracic surgery, CFV should

permit better surgical exposure and a motionless operating field (3,4,7). In low compliance pulmonary disease, CFV should prevent the high inflationary airway pressures with consequent cardiovascular depression and pulmonary barotrauma that can occur during IPPV (3,4,8). Recently, Babinski et al. (7) have reported limited success with CFV in anesthetized patients. They directed a total oxygen flow of $0.6\text{--}0.7\text{ L}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$ through two small tubes placed into the mainstem bronchi with the aid of a flexible bronchoscope. During a 30 min period of CFV, PaCO_2 increased 0.6 mm Hg/min, compared with the 3.8 mm Hg/min that would have occurred during ADO.

Encouraged by the above studies and the successful use of CFV in large dogs in our own laboratory (9), we tested CFV in anesthetized patients for up to 30 min with emphasis on the following features. Because of the high gas inflow rate during CFV, we were concerned that any airway obstruction to expired gas would quickly generate high airway pressures and possibly cause serious barotrauma. We therefore evaluated methods to measure intrathoracic pressure during CFV and we developed a servocontrolled safety system to stop gas inflow if this pressure rises. Separate placement of the bronchial ventilating tubes by

This study was supported by the Universities of Manitoba and Chicago.

Received from the Department of Anesthesia, University of Manitoba, Winnipeg, MB, and the Section of Pulmonary and Critical Care Medicine and the Department of Anesthesia and Critical Care, University of Chicago, Chicago, Illinois. Accepted for publication June 26, 1986.

Address correspondence to Dr. Breen, Department of Anesthesia and Critical Care, University of Chicago, Box 428, 5841 S. Maryland Ave., Chicago, IL 60637.

Table 1. Patient Data

Patient	Age (yr)	Wt (kg)	Operation	Medical status	Smoking	Hb (g/L)	CFV-OTT* (mm ID)
1	23	75	Open reduction of ankle fracture	Moderate alcohol, slight left lower lobe rales	1 pack/day	136	2.5-9.0
2	19	77	Open reduction of femur fracture	Postconcussion and brachial plexus injury		126	2.5-8.0
3	39	94	Excision of anal fistula	Slight morning cough with white sputum	25 pack-year	152	2.5-9.0
4	25	66	Acromioclavicular joint repair	Seizure disorder (see text)	13 pack-years	138	3.5-9.0
5	20	77	Reconstruction of finger	Healthy		141	3.5-9.0, 2.5 tip

*CFV-OTT, constant flow ventilating tubes and orotracheal tube internal diameter (ID) sizes. Constant flow ventilation in patient 5 used 3.5 mm ID tubes, of which the distal 7 mm lengths were constricted to 2.5 mm ID.

a fiberoptic endoscope requires expertise and periods of apnea for the patient. We have designed an orotracheal tube that effects easy and rapid positioning of the bronchial ventilating tubes and provides lateral support to them, without interrupting ventilation of the patient.

Methods

Patient Preparations

After giving informed consent based on a protocol approved by the University of Manitoba Faculty Committee on the Use of Human Subjects in Research, five patients were studied. These patients were undergoing elective surgery, had no significant medical illnesses (Table 1) (American Society of Anesthesiologists physical status class 1 or 2), had normal chest roentgenograms, and were receiving no medications.

After intravenous fentanyl ($1-2 \mu\text{g/kg}$) and diazepam ($50-100 \mu\text{g/kg}$), anesthesia was induced with thiopental, $3.9 \pm 0.7 \text{ mg/kg}$, after which paralysis was produced with pancuronium, $0.090 \pm 0.011 \text{ mg/kg}$. During direct laryngoscopy, 4 ml of 4% lidocaine were sprayed into the trachea, after which a 9.0 mm inner diameter standard orotracheal tube was inserted. Intermittent positive pressure ventilation was begun by means of a standard circle circuit and a volume-cycled ventilator. Inspired oxygen concentration (50-60% nitrous oxide in oxygen) was monitored with an oxygen analyzer (Critikon, Inc., Oxycheek-Model 2000). Exhaled tidal volume ($10.5 \pm 1.5 \text{ ml/kg}$) was measured with a Wright's pattern respirometer (Haloscale model, Ferraris Development and Engineering Co.). Ventilator frequency (8-12 breaths/min) was adjusted to maintain the PaCO_2 near 35 mm Hg.

After induction of anesthesia, we percutaneously introduced a #20 radial arterial catheter to monitor systemic arterial pressure (Psa) continuously and to

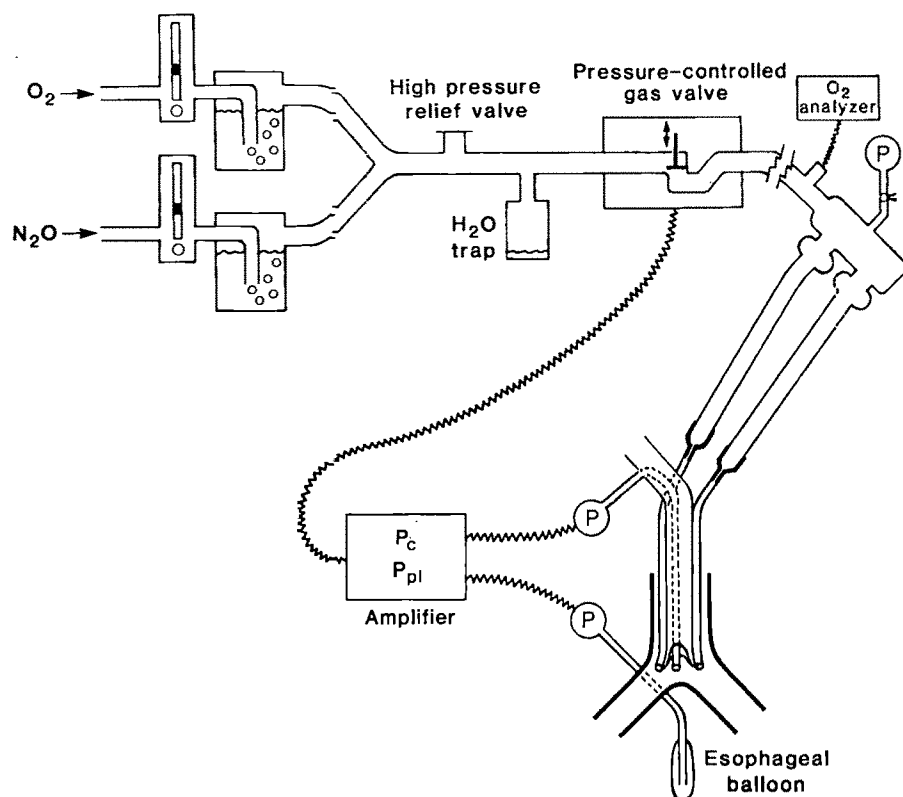
sample blood for measurement of PaO_2 , PaCO_2 , and pHa . A finger pulse oximeter (Bioximetry Technology Inc., Model Biox III) confirmed adequate hemoglobin oxygen saturation. We placed a nasopharyngeal temperature probe and used cutaneous electrodes to monitor neuromuscular blockade. During the study, additional injections of fentanyl (total dose, $7.9 \pm 3.3 \mu\text{g/kg}$), diazepam (total dose, $0.21 \pm .04 \text{ mg/kg}$), thiopental (total dose, $5.3 \pm 1.7 \text{ mg/kg}$), and pancuronium were administered during anesthesia.

Constant Flow Ventilation Circuit (Figure 1)

High airway or pleural pressure caused a solenoid-controlled gas valve to close, thus diverting flow out through a high pressure relief valve (see Appendix I). The oxygen analyzer (Critikon, Inc., Oxycheek-Model 2000) responds to PO_2 , but displays the data as the fraction of inspired oxygen (FiO_2), assuming sea level barometric pressure. Because the pressure in our system was high (approaching two atmospheres) and variable, we used the oxygen analyzer as a trend monitor rather than as an absolute indicator of FiO_2 . Just distal to the oxygen analyzer, an aneroid manometer connected to the patient manifold yielded line pressure. We conducted oxygen and nitrous oxide flow calibrations of the entire circuit while it was connected to the bronchial ventilating tubes (see Appendix II and Figure 2).

To deliver CFV (see also Discussion), we attached intravenous tubing to each side of, and projecting 1-2 cm beyond, the end of a regular cuffless orotracheal tube (OTT). The end of the OTT was notched to provide lateral angulation and distal support to the two bronchial ventilating tubes (Fig. 1). Table 1 lists the calibers of the OTT and the bronchial ventilating tubes used in each patient. We tried to avoid excess intrathoracic pressure by using an OTT with a large lumen to minimize resistance to outflow of gases (10).

Figure 1. Constant flow ventilation circuit: two rotameters (Timeter Instrument Corporation, Model 0-75), factory calibrated between 0 and 75 L/min of oxygen, delivered gas flows through heated humidifiers (Ohio Medical Products, Jet Humidifier). Each humidifier pressure relief valve was closed. Two tubes from the patient manifold were connected through bacterial filters (Respigard) to the right and left bronchial ventilating tubes via pediatric endotracheal tube adapters (2.5 or 3.0 mm inner diameter). Proximal to these adapters, we used 12 mm inner diameter system tubing to minimize resistance to gas flow and therefore circuit pressure. "P" symbolizes a pressure sensor. P_c, carinal airway pressure; P_{pl}, pleural space pressure.



Experiment Protocol

After a 10-min equilibration period of IPPV, we made baseline measurements of heart rate (HR), P_{sa}, and proximal airway pressure and sampled arterial blood for measurements of gas tensions and pH. Then, under direct laryngoscopic view the standard OTT was replaced with the CFV-modified OTT, a silk slip-knot holding the bronchial ventilating tubes together to facilitate rapid atraumatic passage through the vocal cords. Intermittent positive pressure ventilation resumed and through an adapter on the proximal end of the CFV-OTT, the fiberoptic bronchoscope (Olympus Model BF-4B2) was inserted and the carina visualized. The CFV-OTT was advanced and rotated to position each ventilating tube at the orifice of a main-stem bronchus. Carinal pressure was sensed through side-holes in the end of a length of PE-200 tubing, introduced through an adapter on the proximal end of the CFV-OTT (Fig. 1). In one patient, intrapleural pressure (P_{pl}) was also estimated with an esophageal balloon (11). The position of the CFV-OTT was fixed and CFV begun.

At initial total flow rates of 5–10 L/min, the expiratory limb was transiently occluded to dynamically test the airway pressure trace, the audible high pressure alarm, and the pressure-controlled safety valve. Then, we progressively increased flow rates, maxi-

mum flow (0.9–1.6 L·kg⁻¹·min⁻¹) being limited by visual evidence of chest hyperinflation, by an increase in carinal pressure, by an increase in line pressure greater than 600 mm Hg, or by the maximal total rotameter output (120 L/min). F_{IO₂} was adjusted to be near 0.5. Measurements were conducted twice at 5-min intervals, and then variably thereafter (depending on the level of P_{aCO₂}) to a maximum of 30 min of CFV. Then, after confirming its correct position by bronchoscopy, the CFV-OTT was replaced by the standard cuffed OTT and IPPV resumed. After 10 min, IPPV control measurements were repeated and surgery began.

Blood Gas and Data Analysis

Arterial blood and inspired gas samples were analyzed and corrected to the patient's temperature as necessary. To determine the alveolar–arterial P_{O₂} difference (A–aDO₂), P_{AO₂} was calculated by (P_{bar} – 47)(F_{IO₂}) – P_{aCO₂}. Results are expressed as one standard deviation around the mean.

Results

Constant flow ventilation for up to 30 min resulted in hypoventilation of each patient (Fig. 3, top panel).

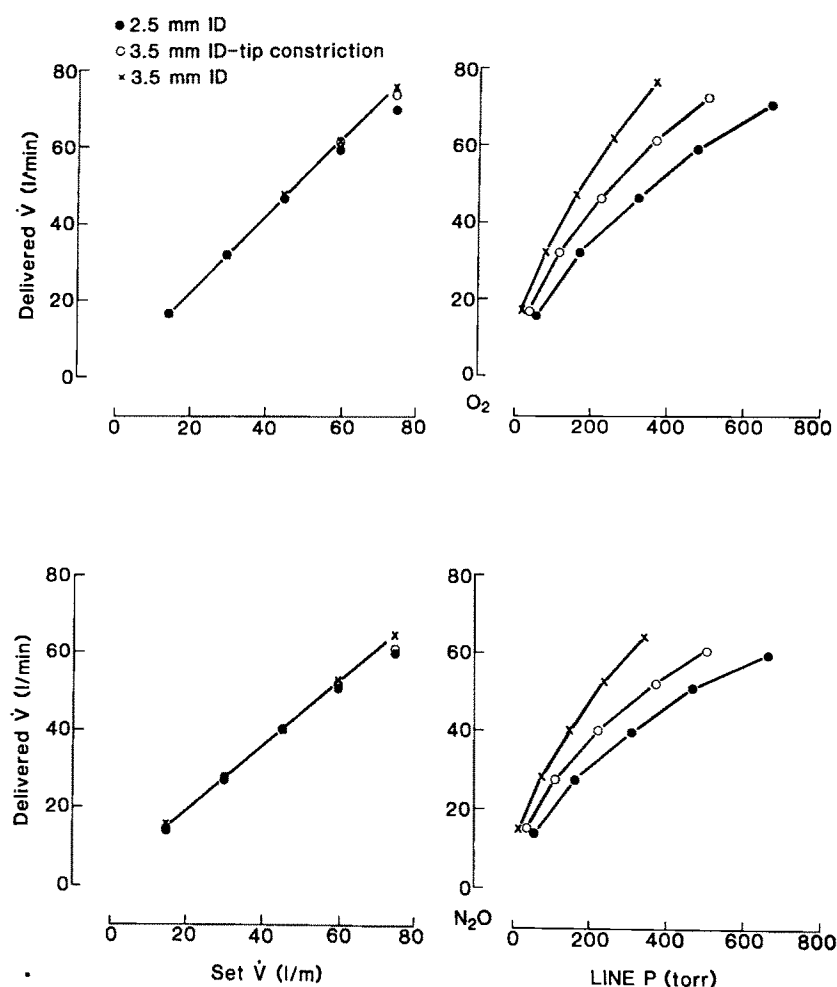


Figure 2. Flow (\dot{V}) calibration of CFV circuit: correlations of delivered (i.e., measured) \dot{V} versus \dot{V} setting (left panels) and delivered \dot{V} versus line pressure (P) (right panels), for oxygen (upper panels) and N_2O (lower panels).

Final P_{aCO_2} during CFV was 49–88 mm Hg compared to 35 ± 3 mm Hg during IPPV. However, the slope of the P_{aCO_2} vs time curve tended to decrease during CFV. For example, in patient 3, P_{aCO_2} increased 2.0 mm Hg/min during the second 5-min period of CFV but then increased only 1.2 and 0.7 mm Hg/min during the second and third 10-min periods of CFV. (Analysis of the increase in P_{aCO_2} with time excludes the first 5-min period of CFV, when there is a temporary exaggerated increase in P_{aCO_2} as mixed venous, alveolar, and arterial P_{CO_2} equilibrate) (6,12). In two patients (1 and 4), P_{aCO_2} actually decreased in the final 5 or 10 min of CFV (to 49 from 60 mm Hg and to 69 from 75 mm Hg).

Arterial pH decreased in all patients during CFV (7.20 ± 0.08) compared with IPPV (7.43 ± 0.05). Although the effects of CFV on arterial PO_2 were variable (Fig. 3, middle panels), two patients (1 and 5) had unexpected decreases in oxygenation.

Compared with IPPV, measured peak carinal pressure decreased during CFV (Fig. 3, bottom panel),

except in patient 2 in whom an 8 mm inner diameter OTT (instead of 9 mm, Table 1) was used during CFV. Yet, during CFV, patients appeared to have high thoracic gas volumes, based on the inspiratory position of the chest wall and low diaphragms. When CFV was stopped, exhalation down to functional residual capacity (FRC) appeared to occur. Particularly in patient 4, the ventilating catheters were initially placed approximately 1 cm into each mainstem bronchus. When CFV began, a marked increase in lung volume appeared to occur and systolic P_{sa} decreased to 80 from 120 mm Hg, necessitating withdrawal of the bronchial catheters to a more proximal position. Average P_{pl} measured in the last patient increased 6 cm H_2O as CFV began; at the same time, peak carinal pressure decreased 9 cm H_2O . There were small, variable changes in HR and P_{sa} during CFV compared with IPPV (Table 2).

Postoperatively, no patient developed respiratory signs or symptoms other than those expected after tracheal intubation (mild sore throat). After surgery,

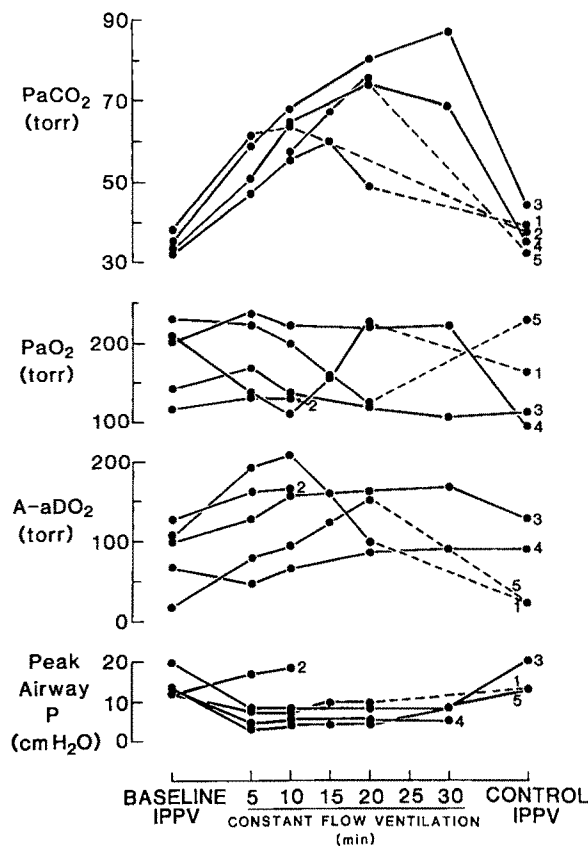


Figure 3. PaCO_2 , PaO_2 , alveolar-arterial PO_2 difference (A-aDO_2), and peak airway pressure during CFV and IPPV. Broken lines indicate that CFV for that patient stopped before 30 min.

patient 4 had a seizure in the recovery room that was attributed to a history of epilepsy not revealed during our prestudy assessment.

Discussion

Although CFV did not maintain normal levels of PaCO_2 in our patients, some alveolar ventilation did occur, as shown by the following analysis of the increase in PaCO_2 during CFV.

Comparison of CFV and Apneic Diffusion Oxygenation

During apneic diffusion oxygenation (ADO), in which oxygen flow is delivered across the proximal opening of a patent airway, no CO_2 elimination occurs (5,6) and average PaCO_2 steadily increases by about 3.8 mm Hg/min (7). In contrast, during the second 5-min period of CFV in our study, the increase in PaCO_2 with

time was only 1.8 ± 0.9 mm Hg/min, reflecting partial CO_2 elimination during this period.

That CFV did wash out CO_2 is supported by estimating the alveolar ventilation (\dot{V}_A) that occurred during CFV using the analysis of Slutsky et al. (6) (See Appendix III). The average \dot{V}_A during CFV (1447 ± 555 ml/min) was $46 \pm 22\%$ of the \dot{V}_A occurring during IPPV (3260 ± 530 ml/min). This lower but effective \dot{V}_A during CFV resulted in the increase to a plateau configuration of the PaCO_2 -time curves (Fig. 3, top pane.). In contradistinction, during ADO there is a progressive linear increase in PaCO_2 with time (6).

An interesting midpoint to this spectrum between ADO (no \dot{V}_A) and CFV (reduced to normal \dot{V}_A) is provided by a study in apneic dogs by Slutsky et al. (6). Low flows of oxygen were introduced through a catheter placed within 1 cm of the carina. At an inflow rate of 0.5 L/min, PaCO_2 increased 2.7 mm Hg/min, corresponding to a calculated 25% of eucapnic alveolar ventilation.

Comparison with Other Studies of CFV

During a similar 30-min period of CFV in five anesthetized patients, Babinski et al. (7) reported a lower average increase in PaCO_2 to 54.9 from 37.0 mm Hg, at about one-half of the total gas flows used in our study. This difference may be due to the 45% greater average body weight of our patients and hence a greater CO_2 production per minute. Therefore, for any given \dot{V}_A effected by CFV, we would predict a greater PaCO_2 increase in our patients. In addition, in contrast to Babinski et al. (7) who positioned the ventilating catheters loose in the mainstem bronchi, we mounted the ventilating tubes onto the sides of a modified endotracheal tube to fulfill patient safety criteria (see below). The resulting larger cross-sectional area of the distal end of our CFV-OTT (Fig. 1) probably required a more proximal positioning of the ventilating catheters to avoid obstruction of exiting gases and consequent hyperinflation of the lungs. This more proximal position of the ventilating catheters relative to the carina is less effective in eliminating CO_2 (1-4,6). Also, any increase in alveolar pressures (hyperinflation) during CFV in our patients may have compressed distal alveolar capillaries, thus decreasing perfusion in ventilated lung units (8,9), impairing CO_2 transfer, and further limiting CO_2 elimination.

Why, in contrast to humans, does CFV successfully maintain normocarbica in animals (2-4,9)? First, relative to their body weight (and thus CO_2 production), dogs have larger main airways than humans, which facilitates normal levels of \dot{V}_A . Light nitrous ox-

Table 2. Mean Arterial Blood Pressure and Heart Rate during CFV and IPPV

Patient	IPPV Baseline		CFV (min)										IPPV Control	
	Psa ^a	Hr ^b	Psa	HR	Psa	HR	Psa	HR	Psa	HR	Psa	HR	Psa	HR
1	88	60	73	60	71	65	85	66	85	72	—	—	90	67
2	88	92	89	87	87	84	—	—	—	—	—	—	92	78
3	75	62	78	67	78	67	—	—	73	74	98	79	75	62
4	77	78	—	80	87	82	—	—	83	87	88	89	86	72
5	95	64	87	67	88	66	95	57	110	57	—	—	103	56
Mean \pm SD (n = 4)	84 \pm 9	66 \pm 8			81 \pm 8	70 \pm 8			88 \pm 16	73 \pm 12			89 \pm 12	64 \pm 7

Abbreviations: CFV, constant flow ventilation; IPPV, intermittent positive pressure ventilation; Psa, mean arterial blood pressure; HR, heart rate.

^aValues are in mm Hg.^bValues are min⁻¹.

ide/narcotic anesthesia theoretically might have increased the metabolic rate and thus the CO₂ production in our patients, compared to barbiturate anesthesia in the canine studies (2,4), but this is unlikely because we paralyzed our patients (to ensure apnea during the period of CFV) and thus eliminated respiratory and other muscle work (13). Second, the multiple inert gas analysis during CFV demonstrates a widened distribution of V/Q ratios in the canine lung (14), and streaming effects at lobar bronchial bifurcations may add to ventilation inhomogeneity among lobes (9). We speculate that our patients were at even more risk for ventilatory inhomogeneity than dogs because human lungs have less pronounced collateral channels for ventilation between distal lung units (15) and the alveolar pressure may have been greater during CFV in our patients than in our dogs (9,14).

Carbon dioxide elimination may be directly related to carinal gas flow (2,9). Because the degree of gas mixing and thus CO₂ removal must be ultimately related to the total amount of energy delivered (E) to the respiratory apparatus, we considered that E might be better enhanced by increasing gas velocity (v) rather than flow ($E = \frac{1}{2}mv^2$, where m is the mass of gas (flow) delivered to the carina). Thus, we tried bronchial ventilating catheters with different lumen sizes and tip orifices (Table 1). We chose the larger 3.5 mm inner diameter tube to minimize the pressure required to drive flow and a catheter tip constriction to decrease the cross-sectional area and thus increase gas velocity. However, in the experience of Slutsky et al. (6), decreasing catheter orifice size did not seem to improve CO₂ elimination. Conceivably, other ventilating catheter tip configurations (e.g., numerous small side holes) might augment gas mixing and thus CO₂ elimination.

Effect of CFV on Oxygenation

The decrease in PaO₂ during CFV in two of our patients may also have resulted from V/Q inequality (9,10) or even from true shunt caused by scattered atelectasis. This scattered atelectasis might result from inhomogeneity of distending pressure in the lung (9). Alternatively, the increase in alveolar pressure may have decreased venous return, cardiac output, and thus mixed venous PO₂.

Interpretation of Carinal Pressure during CFV

At the onset of CFV, despite a decrease in carinal pressure, CFV appeared to increase FRC. This change in FRC seems to result from two factors. First, bidirectional flow at the carina may reduce the effective cross-sectional area available to outflowing gas. Thus resistance to this exiting gas flow is increased, requiring a greater driving pressure (alveolar distending pressure) (10). Second, and to a smaller degree, the Venturi principle means that distal airspace gas with velocity near zero has a greater pressure than carinal gas, which has a high velocity (8,10). We also found (in one patient) that a change in esophageal pressure more accurately reflects a change in FRC than carinal pressure sensing and also avoids the problem of carinal catheter tip malposition.

Accordingly, low intratracheal pressures reported in animal studies of CFV (2) must be interpreted with caution, unless that pressure is either measured at zero flow achieved by synchronous clamping of inflow and outflow lines (3) or validated by simultaneous monitoring of alveolar pressure by intrapulmonary needles (9). Yet, once CFV is established with

stable gas inflow rates, changes in proximal airway pressure should accurately reflect changes in alveolar pressure; thus carinal pressure is still a valid indicator to detect lung inflation and thus to trigger the safety solenoid valve to interrupt flow into the lungs.

Clinical Role of CFV

The study of Babinski et al. (7) suggests that CFV might be clinically applicable during thoracic surgery where organ movement associated with normal mechanical ventilation is undesirable. During 30 min of CFV in the Babinski et al. study, oxygenation remained good and PaCO_2 rose moderately but still remained within the clinically useful range (54.9 ± 4.0 mm Hg). We believe that our study strongly tempers these conclusions, in several ways.

We cannot overemphasize the potential hazards to the patient when high gas flows are introduced into the airways. Any obstruction to outflowing gas could cause overinflation of the lungs within seconds with subsequent alveolar rupture, pneumothorax, and possible pulmonary venous air embolism. We developed a pressure-controlled gas valve system to immediately interrupt gas flow to the patient if intrathoracic pressure rose above a preset level (see Appendix I). Babinski et al. (7) did not report the use of safety devices to protect their patients from pulmonary overinflation. Even in potential ventilating systems using much lower flow rates (6), a similar safety system incorporating appropriate pressure sensors seems prudent in case a ventilating catheter occludes a distal and smaller airway.

Safety considerations are also important in the design of the bronchial ventilating catheters. In one preliminary experiment and in two study patients, we placed the bronchial ventilating tubes and a carinal pressure catheter with the aid of introducing wires and a fiberoptic bronchoscope. Difficulty in accurate, consistent, and stable placement of these catheters without traumatizing the upper or lower airway and concern that lack of support to the ventilating catheters in the airways would allow oscillations of the catheter tips (observed during bench testing) and result in mucosal erosion (16) prompted us to develop our modified endotracheal tube. In addition to minimizing the above problems, this CFV-OTT facilitated orotracheal intubation, bronchoscopy to verify its proper position without significant apnea, and stabilization at the mouth to prevent migration of the ventilating tubes into distal, smaller airways. (A modified Carlen's double-lumen endotracheal tube has been used to deliver CFV in dogs (3). We avoided this

system in patients because the luminal caliber is small (causing resistance to exiting gases and precluding endoscopy to confirm position at the carina) and the carinal hook incorporated into the double-lumen tube can traumatize the airway.)

Yet constant carinal gas flow does effect some alveolar ventilation in patients. Indeed, mechanisms resulting in the gas mixing during CFV (2) may contribute to effective alveolar ventilation whenever gas flows are introduced near the carina, such as during high flow catheter ventilation for airway surgery (17). We suggest that lower carinal flows, which would minimize the potential for airway trauma, could be delivered in concert with IPPV, as demonstrated in a recent report in dogs with acute pulmonary edema (18) and analogous to a clinical study of combined high frequency ventilation during respiratory failure (19). Both by reducing dead space and by augmented gas mixing, this carinal flow could permit reduction in tidal volume during IPPV. This system would minimize respiratory movement during thoracic surgery (7), and would reduce inspiratory pressures and thus minimize pulmonary barotrauma and cardiovascular depression in pulmonary edema (8).

Appendices

Appendix I

Pressure-Controlled Safety Valve System. We modified a current Hewlett-Packard patient monitoring system to utilize both the existing high and low alarm limits provided with each pressure channel and the electrical safety standards incorporated into clinical equipment. The radial arterial catheter, the carinal airway catheter, and, in patient 5, the esophageal balloon were attached to pressure transducers (Hewlett-Packard Model 1280-C) and amplifiers (HP Model 732C5-B). These pressure amplifiers and the ECG amplifier (HP Model 78203-A) were housed in a 4-channel main frame (HP Model 78901-A) and oscilloscope display (HP Model 78302-A). The carinal and pleural pressure amplifiers were modified so that their alarms could not be disarmed. We accessed the HP alarm circuit to provide an electrical signal to the solenoid-actuated gas valve (Airmatic Allied Model 250X-8). If either airphase pressure signal exceeded a preset limit, the alarm signal actuated a relay, de-energized and closed the solenoid valve, and diverted gas flow from the patient to the atmosphere through the high pressure relief valve (500 mm Hg opening threshold) (back-bar assembly, BOC Boyle International Anesthesia Machine). In addition, the standard 5-sec alarm delay

for a high pressure limit was changed to less than 0.25 sec to achieve rapid enough response time for closing the valve. A slight time delay was necessary to prevent transient pressure spikes (such as produced by touching the tubing) from triggering the alarm.

Appendix II

Flow Calibration of the CFV Circuit. At usual operating line pressure, we used a dry gas meter (American Meter Co., Philadelphia, Model 802) to calibrate the complete CFV circuit for the three sizes of bronchial ventilating catheters. The left panels of Figure 2 depict measured flow versus set flow for oxygen (upper panels) and nitrous oxide (lower panels). For the large caliber ventilating tubes, the flow meter delivered accurate flows of oxygen ($m = 0.973$, $b = 2.5$, $r = .999$) and linear but underestimated flows of nitrous oxide ($m = 0.827$, $b = 2.5$, $r = 0.999$). However, for the two smaller calibers of ventilating tubes, delivered flow was less for both oxygen ($\leq 9\%$) and nitrous oxide ($\leq 8\%$) at high rotameter flow settings. We noted that the high line pressure required to drive high flow through the smaller caliber ventilating tubes would sometimes cause small leaks through the high pressure relief valve (Fig. 1), and thus decrease delivered flow. Therefore, we also calibrated delivered flow against line pressure (right panels, Fig. 2). Line pressure was sensed immediately proximal to the ventilating tubes (constant physical resistance characteristics) and was thus a unique curvilinear function of delivered flow. By correlating the line pressure generated at a particular set flow for all CFV periods, we confirmed that no significant overestimation of delivered flow was occurring.

Appendix III

Estimation of Alveolar Ventilation before Equilibrium. In our study, alveolar ventilation (\dot{V}_A) during CFV was less than the eucapnic level during IPPV and therefore P_{aCO_2} increased with time towards an equilibrium plateau (Fig. 3, top panel). Because characteristics of CFV (especially gas inflow rates) were relatively constant during the entire period of CFV for each patient, we assume a relatively constant \dot{V}_A . Therefore, for each patient we averaged the values of \dot{V}_A generated from the different segments of the P_{aCO_2} vs time curve (Fig. 3), excluding the first 5 min of CFV during which there is a temporary exaggerated increase in P_{aCO_2} as mixed venous, alveolar, and arterial PCO_2 equilibrate (6,12).

To estimate \dot{V}_A during CFV we used the following equation developed by Slutsky et al. (6):

$$dPCO_2/dt = [\dot{V}_{CO_2} - K(dPCO_2/dt)] P_B/FRC - (P_B/(P_B - 47)) \dot{V}_A PCO_2/FRC$$

where functional residual capacity (FRC) is estimated from body height (20) and \dot{V}_{CO_2} is estimated from body weight ($2.4 \text{ ml} \cdot \text{min}^{-1} \cdot \text{kg}^{-1}$). K is estimated for each patient by solving the equation after setting \dot{V}_A equal to zero (i.e., apneic diffusion oxygenation) and then assuming $dPCO_2/dt$ (after initial equilibration) to be 3.0 mm Hg/min (12). Using this value for K , the equation can then be solved for \dot{V}_A using the slope ($dPCO_2/dt$) of the P_{aCO_2} vs time curve at a particular value of P_{aCO_2} .

Two patients (1 and 4) had plateaus in their P_{aCO_2} vs time curves, reflecting equilibration between pulmonary elimination and metabolic production of CO_2 . At this steady state, the ventilation relationship

$$P_{aCO_2} = (\text{constant})(\dot{V}_{CO_2})/(\dot{V}_A)$$

can be rearranged to give the final P_{aCO_2} expected for a given \dot{V}_A during CFV

$$(P_{aCO_2}[IPPV])(\dot{V}_A[IPPV])/(\dot{V}_A[CFV]).$$

In patients 1 and 4, the calculated final values of P_{aCO_2} (49 and 72 mm Hg respectively) were close to the measured values (49 and 69 mm Hg).

The writers thank J. L. Sala, Biomedical Engineering Department and J. Longmuir, Department of Anesthesia, University of Manitoba; and C. Becker, L. Becker, and G. Crawford, University of Chicago for their expert technical assistance. We also thank Dr. A. Slutsky, Department of Medicine, University of Toronto for his advice on calculating alveolar ventilation during CFV; and Dr. M. Roizen, Department of Anesthesia and Critical Care, University of Chicago and Dr. R. Palahniuk, Department of Anesthesia, University of Manitoba for their reviews of our manuscript. We are grateful to A. Wildeman, Ohmeda Canada for the use of the finger pulse oximeter.

References

1. Meltzer SJ, Auer J. Continuous respiration without respiratory movements. *J Exp Med* 1909;11:622-5.
2. Lehnert BE, Oberdorster G, Slutsky AS. Constant-flow ventilation of apneic dogs. *J Appl Physiol: Respirat Environ Exercise Physiol* 1982;53:483-9.
3. Chakrabarti MK, Whitwam JG. Pulmonary ventilation by continuous flow using a modified Carlen's tube. *Crit Care Med* 1984;12:354-6.
4. Smith RB, Babinski M, Bunegin L, Gilbert J, Swartzman S, Dirting J. Continuous flow apneic ventilation. *Acta Anaesthesiol Scand* 1984;28:631-9.
5. Holmdahl MH:SON. Pulmonary uptake of oxygen, acid-base

- metabolism, and circulation during prolonged apnoea. *Acta Chir Scand (Suppl)* 1956;212:421-4.
6. Slutsky AS, Watson J, Leith DE, Brown R. Tracheal insufflation of O₂ (TRIO) at low flow rates sustains life for several hours. *Anesthesiology* 1985;63:278-86.
 7. Babinski MF, Sierra OG, Smith RB, Leano E, Chavez A, Castellanos A. Clinical application of continuous flow apneic ventilation. *Acta Anaesthesiol Scand* 1985;29:750-2.
 8. Breen PH, Ali J, Wood LDH. High-frequency ventilation in lung edema: effects on gas exchange and perfusion. *J Appl Physiol* 1984;56:187-95.
 9. Wood LDH, Nahum A, Schumacker PT, Sznajder JI. Flow dependence of gas exchange and regional lung volume during constant flow ventilation (abstr). *Am Rev Respir Dis* 1985;131:A314.
 10. Nahum A, Sznajder JI, Wood LDH. Airway and regional alveolar pressures in constant flow ventilation (CFV) (abstr). *Fed Proc* 1985;44:1384.
 11. Higgs BD, Behrakis PK, Bevan DR, Milic-Emili J. Measurement of pleural pressure with esophageal balloon in anesthetized humans. *Anesthesiology* 1983;59:340-3.
 12. Eger EI, Severinghaus JW. The rate of rise of P_ACO₂ in the apneic anesthetized patient. *Anesthesiology* 1961;22:419-25.
 13. Viires N, Sillye G, Aubier M, Rassidakis A, Roussos C. Regional blood flow distribution in dog during induced hypotension and low cardiac output. *J Clin Invest* 1983;72:935-47.
 14. Schumacker PT, Sznajder JI, Nahum A, Wood LDH. Gas exchange during constant flow ventilation (CFV) (abstr). *Fed Proc* 1985;44:1896.
 15. Woolcock AJ, Macklem PT. Mechanical factors influencing collateral ventilation in human, dog, and pig lungs. *J Appl Physiol* 1971;30:99-115.
 16. Ophoven JP, Mammel MC, Gordon MJ. Tracheo-bronchial histopathology associated with high-frequency jet ventilation. *Crit Care Med* 1984;12:829-32.
 17. McClish A, Deslauriers J, Beaulieu M et al. High-flow catheter ventilation during major tracheobronchial reconstruction. *J Thorac Cardiovasc Surg* 1985;89:508-12.
 18. Sznajder JI, Becker CJ, Burgett J, Crawford G, Wood LDH. Combination of constant flow (CF) and continuous positive pressure ventilation (CPPV) improves management of pulmonary edema (abstr). *Am Rev Respir Dis* 1985;131:A141.
 19. El-Baz N, Faber LP, Doolas A. Combined high-frequency ventilation for management of terminal respiratory failure: a new technique. *Anesth Analg* 1983;62:39-49.
 20. Cherniack RM. *Pulmonary Function Testing*. Philadelphia: WB Saunders, 1977:244.

The In Vitro and In Vivo Effects of Isoflurane and Nitrous Oxide on Platelet Aggregation

Brent G. Fauss, MD, James C. Meadows, MD, Christine Y. Bruni, BS, and
G. D. Qureshi, MD

FAUSS BG, MEADOWS JC, BRUNI CY, QURESHI GD.
The in vitro and in vivo effects of isoflurane and nitrous oxide on platelet aggregation. *Anesth Analg* 1986;65:1170-4.

In view of the possible antiaggregation effects of newer general anesthetics we investigated the in vitro and in vivo effects of isoflurane and nitrous oxide on platelet aggregation. Platelets obtained from 18 healthy volunteers, were exposed in vitro for 30 min in a closed chamber to oxygen-carbon dioxide (90%,5%) (control), oxygen-carbon dioxide-nitrous oxide (80%), or oxygen-carbon dioxide-isoflurane (1.5%) with or without nitrous oxide (80%). Samples were tested in ADP- and collagen-induced aggregation tests.

Both nitrous oxide and isoflurane produced statistically significant inhibition of ADP-induced aggregation. Inhibition of collagen-induced aggregation was not statistically significant. In 18 patients who received nitrous oxide (3 L/min) and isoflurane (1-2%) during anesthesia, platelet aggregation was reduced significantly. We conclude that both nitrous oxide and isoflurane cause moderate but statistically significant inhibition of platelet aggregation that may be clinically important in some patients.

Key Words: BLOOD—platelets. ANESTHETICS, VOLATILE—isoﬂurane. ANESTHETICS, GASES—nitrous oxide.

Abnormalities of platelet hemostasis pose increased risk to patients undergoing anesthesia and surgery. Anesthetic agents may, like many other drugs, alter platelet function in vivo. Various volatile anesthetics such as halothane and enﬂurane have been shown to inhibit platelet function (1,2). Ueda et al. (3) reported inhibition of canine platelet aggregation by methoxyﬂurane, halothane, diethyl ether, and cyclopropane when tested at clinically comparable partial pressures. Other investigators have reported varied effects of anesthetic agents on platelet aggregation (1,2,4-7). The effects of newer anesthetics such as isoflurane on platelet aggregation have not yet been studied. In this paper we report the in vitro and in vivo effects of isoflurane and nitrous oxide on platelet aggregation.

Methods and Materials

Materials

We used isoflurane (Forane®) obtained from Anaquest, (Madison, WI), and nitrous oxide and oxygen supplied by Airco Medical Gases (Murray Hill, NJ). The aggregating agents, adenosine diphosphate (ADP) and collagen (Bovine tendon), were purchased from Sigma Chemical Company (St. Louis, MO).

Collection of Blood Samples

After obtaining informed consent, venous blood samples (25-30 ml) were obtained in 3.8% sodium citrate anticoagulant (blood to anticoagulant ratio 9:1) from seventeen healthy volunteers as previously described (8). Donors with a history of platelet-inhibiting drugs such as alcohol, acetylsalicylic acid, nonsteroidal antiinflammatory agents, antihistamines, tricyclic antidepressants, and antibiotics 10 days prior to the study were excluded.

Preparation of Platelet-Rich Plasma and Platelet-Poor Plasma

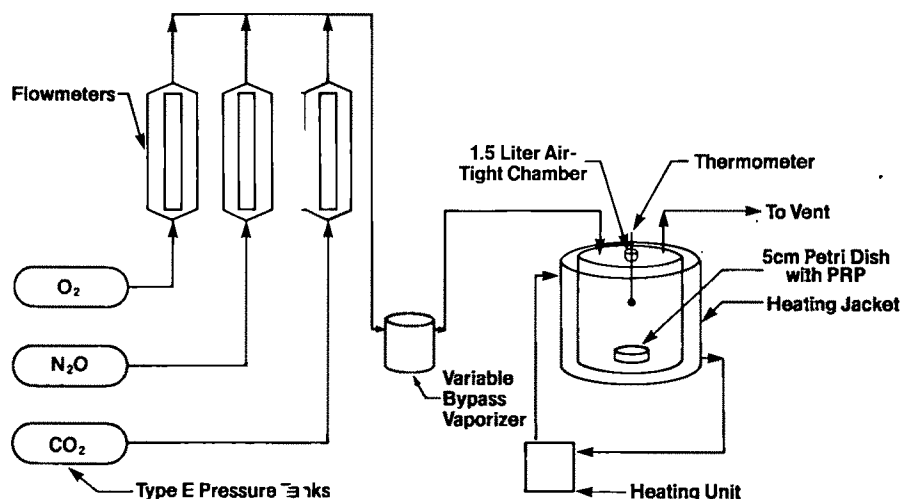
Blood samples were centrifuged (1200 xg, 3 min, 25°C) to isolate platelet-rich plasma (PRP) contained in the supernate. The remainder of the blood was recentri-

Supported by VCU School of Medicine, Small Grant Program, and Department of Anesthesia, Medical College of Virginia, Richmond, Virginia.

Received from the Departments of Anesthesia, Pathology, and Medicine, Medical College of Virginia, Richmond, Virginia. Accepted for publication May 21, 1986.

Address correspondence to Dr. Qureshi, Box 297, Medical College of Virginia, Richmond, VA 23298.

Figure 1. Experimental apparatus used for in vitro exposure of platelets to volatile anesthetic agents. Platelet-rich plasma was placed in an airtight chamber enclosed in a heating jacket. The chamber temperature was monitored and maintained according to experimental design described in the text. The rate of flow of oxygen, carbon dioxide, and nitrous oxide were determined by flow meters. Isoflurane concentration was controlled by a variable bypass vaporizer.



fused (1200 xg, 20 min, 25°C) to prepare platelet-poor plasma (PPP) as previously described (9). The PRP was diluted with the native PPP to yield test PRP with a final platelet count of $1.5\text{--}2.0 \times 10^5/\mu\text{l}$.

Platelet Aggregation Studies

Platelet aggregation was studied by the turbidimetric technique of Born (15) on a Bio-Data PAP-2 Aggregometer (Dela Corporation, Rockville, MD). The aggregating agents used were ADP (2.5–5.0 μM) and collagen (0.19 or 0.08 mg/ml). The platelet aggregation mixture, which was composed of 450 μl of the test PRP, was incubated in a closed chamber containing the test anesthetics under experimental conditions described below. The aggregation response was recorded for 7 min after the addition of ADP or collagen (50 μl). Each aggregation test was performed in duplicate and the control sample was repeated after every third test. All aggregation studies were completed within 2–3 hr of blood collection.

In Vitro Exposure of Platelets to Volatile Anesthetic Agents

Platelets contained in PRP were exposed to isoflurane or nitrous oxide by the following techniques: a 3.5 ml aliquot of the PRP was added to a plastic petri dish (5 cm diameter) and placed in an airtight chamber (see Figure 1). A mixture of humidified oxygen (90%) and carbon dioxide (5%) flowed through the chamber for 30 minutes at room temperature. A carbon dioxide flow rate of 50–70 ml/min maintained the pH of the

test PRP in the 7.3–7.5 range. Without the carbon dioxide the pH in the test samples increased from 7.5 to 3.5 in 1 hr. This finding agrees with the observation of Collier et al. (10), who found it necessary to supplement carbon dioxide to maintain pH in the PRP preparation. The platelet samples were exposed to a mixture of humidified oxygen and carbon dioxide with or without isoflurane (1.5%) for 30 min in the chamber described above. After 30 min 0.45 ml of PRP sample was withdrawn and transferred to aggregometer and platelet aggregation measured. The PRP samples were kept capped during the transfer and platelet aggregation studies. In another study nitrous oxide (80%) was added to both the oxygen/carbon dioxide gas mixture and the experimental oxygen/carbon dioxide/isoflurane mixture. In these studies 0.45 ml of PRP that was incubated in the chamber capped without exposure to anesthetic gases served as control. The platelet-rich plasma mixture was incubated at 37°C for 1 min prior to the addition of aggregating agents.

Platelet Aggregation Studies after In Vivo Exposure to Isoflurane and Nitrous Oxide

In order to study the in vivo effects of isoflurane and nitrous oxide on platelet function, venous blood was obtained from nine patients undergoing elective surgery before (control) and one half hour after induction of general anesthesia using an intravenous administration of fentanyl (1.5 $\mu\text{g/kg}$), methohexital (1.5 mg/kg), *d*-tubocurarine (0.04 mg/kg), and succinylcholine (1.5 mg/kg). Anesthesia was maintained with isoflurane (1–2%) in a mixture of nitrous oxide (3 L/min) and oxygen (2 L/min). Blood samples were capped after

Table 1. Effect of Isoflurane on Platelet Aggregation In Vitro

Test Mixture	Group (n)	Platelet aggregation (%)	
		ADP (5 μ M) (mean \pm SE)	Collagen (190 μ g/ml) (mean \pm SE)
Control platelets ^a	A (16)	75.9 \pm 1.6	ND
Platelets exposed to O ₂ -CO ₂	B (18)	73.4 \pm 2.2	75.0 \pm 1.4
Platelets exposed to O ₂ -CO ₂ -isoflurane	C (18)	69.2 \pm 2.3	74.8 \pm 1.6

Abbreviation: ND, not done.

P value comparisons: B vs A, not significant; C vs A, *P* < 0.05; B vs C, *P* < 0.05.^aUnexposed to anesthetic gases.

withdrawal of blood and during the platelet aggregation studies using ADP and collagen as described above.

Analysis of the Data

Platelet aggregation was expressed as percent aggregation (height of aggregation wave) in response to the aggregating agents tested. For each test a minimum of two values were generated. The data were analyzed using an analysis of variance statistic *F* test (11).

Results

Table 1 shows the in vitro effects of isoflurane on platelet aggregation. The data are expressed as the percent platelet aggregation (mean \pm SE) of 18 samples obtained from nine patients using ADP (5 μ M) as aggregating agent. The percent aggregation of platelets unexposed to anesthetic gases was 75.9 \pm 1.6, whereas upon exposure to oxygen-carbon dioxide (90%, 5%) percent aggregation was 73.4 \pm 2.2%. Similarly, after 30 min exposure to oxygen/carbon dioxide/isoflurane (1.6%) the percent platelet aggregation was 69.2 \pm 2.3%. The difference in aggregation results between platelets unexposed to any anesthetic gases and platelets exposed to oxygen-carbon dioxide (*P* > 0.05) was not statistically significant, whereas a significant difference in platelet aggregation (*P* < 0.05) was observed between percent aggregation of platelets exposed to oxygen-carbon dioxide and platelets exposed to oxygen-carbon dioxide-isoflurane. Using collagen as an aggregating agent, the percent aggregation of platelets after exposure to oxygen-carbon dioxide was 75.0 \pm 1.4%, and after oxygen-carbon dioxide-isoflurane percent aggregation was 74.8 \pm 1.6%. The difference between these values was not statistically significant: *P* > 0.10; *F* ratio, 0.04. In-

Table 2. Effect of Isoflurane and Nitrous Oxide on Platelet Aggregation In Vitro

Test mixture	Group (n)	Platelet aggregation (%)	
		ADP (5 μ M) (mean \pm SE)	Collagen (80.8 μ g/ml) (mean \pm SE)
Control platelets ^a	A (16)	70.2 \pm 2.3	ND
Platelets exposed to O ₂ -CO ₂ -N ₂ O	B (16)	58.3 \pm 2.9	86.1 \pm 1.5
Platelets exposed to O ₂ -CO ₂ -N ₂ O-isoflurane	C (38)	60.1 \pm 2.1	88.8 \pm 1.7

Abbreviation: ND, not done.

P value comparisons: B vs A, *P* < 0.05; C vs A, *P* < 0.05; C vs B, not significant.^aUnexposed to anesthetic gases.

ing the concentration of isoflurane in one sample to 5% did not proportionately increase inhibition of ADP-induced aggregation. Again collagen-induced aggregation remained unaffected (data not shown).

In the second study we examined the effect of isoflurane in the presence of nitrous oxide on platelet aggregation. Sixteen samples from eight patients (two samples from each patient) were examined using ADP (5 μ M) as an aggregating agent (Table 2). The percent aggregation in control (no gas flow) was 70.2 \pm 2.3%, with oxygen-carbon dioxide-nitrous oxide 58.3 \pm 2.9%, and with oxygen-carbon dioxide-nitrous oxide-isoflurane 60.1 \pm 2.1%. A pairwise comparison of the results obtained with the three gaseous combinations using a Bonferroni *t*-test showed that nitrous oxide caused significantly more inhibition of platelet aggregation. The addition of isoflurane to the gas chamber did not further affect the mean percentage of platelet aggregation (*P* > 0.05). When collagen (80.8 μ g/ml) was used as the aggregating agent, the percent aggregation after exposure to oxygen-carbon dioxide-nitrous oxide was 86.1 \pm 1.5%, and the percent aggregation after exposure to oxygen-carbon dioxide-nitrous oxide-isoflurane was 88.8 \pm 1.7%. The difference between these values is not significant (*F* ratio, 2.71; *P* > 0.10).

In the in vivo study (Table 3) the percent aggregation before induction of anesthesia using ADP, 5 μ M, ADP, 10 μ M, or collagen, 80.8 μ g/ml, were 48.2 \pm 2.6%, 58.6 \pm 2.2%, and 72.8 \pm 2.3%, respectively. After exposure to isoflurane and nitrous oxide for 30 min in vivo, the percent platelet aggregations with ADP and collagen were 44.0 \pm 2.5%, 54.9 \pm 2.2%, and 68.1 \pm 4.4%, respectively. These results show a statistically significant difference between platelet aggregation before and after exposure to general anesthesia using two different concentrations of ADP

Table 3. Platelet Aggregation Studies in Patients Before and After 30 Min Exposure in Vivo to Isoflurane and Nitrous Oxide

Test mixture	n	Platelet aggregation (%)		
		ADP (5 μ M) (mean \pm SE)	ADP (10 μ M) (mean \pm SE)	Collagen (80.8 μ g/ml) (mean \pm SE)
Control platelets (before anesthesia)	18	48.2 \pm 2.6	58.6 \pm 2.2	72.8 \pm 2.3
Platelets exposed to isoflurane-nitrous oxide in vivo	18	44.1 \pm 2.5 ^a	54.9 \pm 2.2 ^b	68.1 \pm 4.4 ^c

^a $P < 0.03$.^b $P < 0.005$.^cNot significant.

($P < 0.03$ and $P < 0.005$). However, there was no statistically significant difference when collagen was used as the aggregation agent.

Discussion

Our understanding of the role of platelets in primary hemostasis has greatly expanded in the last few years. After endothelial injury the platelets undergo a series of changes including adhesion, shape change, degranulation, and aggregation to participate in the formation of a hemostatic plug. (12-14). The clinical evaluation of primary hemostasis is best achieved in vivo by a skin bleeding time test, whereas an in vitro platelet aggregation test is considered to be a sensitive measure of platelet function (15,16).

Several drugs have been demonstrated to inhibit platelet aggregation in vitro. While studying the effect of a drug on platelet aggregation it is, of course, essential to establish that the platelets have been adequately exposed to the drug. Adequate exposure is especially a consideration in the case of volatile anesthetics that at ambient atmospheric pressure may not achieve equilibrium with platelets suspended in the liquid phase of platelet-rich plasma. To overcome this difficulty we designed a closed chamber (Fig. 1) in which platelets were exposed to volatile anesthetics assuring a specific drug concentration in equilibrium with platelets. Our preliminary studies suggested that a 30 min exposure of platelets to the test agent was adequate to achieve equilibrium. In addition, the closed chamber also permitted the introduction of carbon dioxide to maintain the PRP sample at a physiological pH of 7.2-7.5, which has been shown to be an important variable affecting the in vitro platelet aggregation test (10).

In our in vitro studies both nitrous oxide (80%) and isoflurane (1.5%) demonstrated small but statistically significant inhibition of ADP-induced platelet aggregation (Tables 1 and 2). The inhibition was rapid in onset (30 min) and occurred because of a direct effect of the anesthetic agent on the platelets. The in vitro

design of our experiments permitted a direct exposure of platelets to the drugs and thus allowed us to exclude multiple variables of in vivo experimentation such as species specificity, variability of drug kinetics and drug metabolism, effect of concomitant drugs, associated illnesses, and surgical procedures. In addition, using our specially designed experimental chamber we were able to achieve a better control of drug concentration, temperature, and pH in the test samples. It is interesting to note that in these experiments the addition of isoflurane to the mixture of oxygen, carbon dioxide, and nitrous oxide did not affect the percent inhibition by nitrous oxide alone. We postulate that in the presence of nitrous oxide the platelet agonist receptor sites may have been fully saturated thus making these sites unavailable for isoflurane. However, this hypothesis remains to be tested. In our in vivo study on patients who received isoflurane and nitrous oxide during surgery, a small but statistically significant inhibition of platelet aggregation was also observed. Because these patients received several drugs in addition to the anesthetic agents during the induction, it is difficult to exclude completely the effect of preanesthesia drugs and/or surgery on our observed results. In a previous study, O'Brien et al. (5) were unable to show any effect of many of the induction drugs including meperidine, atropine, hyoscine papaveretum, neostigmine, tubocurarine, succinylcholine, methohexital, and thiopental on the platelet aggregation. Whether surgical procedures inhibit platelet aggregation in the absence of anesthetic agents or premedication is not known. The mechanism of the lack of significant inhibition of collagen-induced aggregation in both studies with nitrous oxide and isoflurane is not clear. These effects were observed in both in vitro and in vivo studies. Because the percent aggregation in control platelets using two different concentrations of collagen were within normal limits (Tables 1 and 2), it seems unlikely that the observed results could be attributed to variability of our test collagen preparation. We believe that the discrepancy between the results of ADP- and

collagen-induced aggregation in our study can be best explained on the basis of the difference of platelet sensitivity to different aggregating agents. Platelets are inherently more sensitive to ADP (17) and thus a small inhibitory effect of a drug may be more obvious in ADP aggregation than in collagen aggregation. Similar discrepancy of platelet aggregation with different aggregating agents has also been observed in diseases such as chronic myeloproliferative syndrome (18-20) and is most likely due to the same reasons.

A review of the current literature suggests that the effects of isoflurane and nitrous oxide on platelet aggregation have not been examined previously. However, the effects of other volatile anesthetics such as halothane and enflurane have been previously reported (2,6). Using human platelets, Dalsgaard-Nielsen and Gormsen found a decrease in platelet aggregation in vitro with halothane when ADP, epinephrine, and collagen were used as aggregating agents (2). In another study (6), there was an increase in platelet aggregation when liquid halothane was added directly to the test PRP. The investigators claimed that halothane potentiated the ADP aggregation response. In several in vivo studies (4-6,9) the results of the effect of enflurane, nitrous oxide, and oxygen on platelet aggregation have been variable. Gotta et al. observed no significant alteration of platelet aggregation (ADP- and collagen-induced) in 30 patients undergoing major surgical operations using either nitrous oxide-oxygen-enflurane or nitrous oxide-oxygen-fentanyl as anesthetics (1). Lichtenfeld et al., who examined the effect of nitrous oxide, enflurane, and halothane on platelet aggregation in 12 patients undergoing minor surgery, observed only a slight inhibition of platelet aggregation (ADP and collagen) in two of their patients using preoperative values as controls (4). Thus, the results of the studies on the effect of general anesthetics on platelet function had been variable.

The clinical significance of our in vitro and in vivo observations is not known at this time. Our experience in a large number of patients who received isoflurane and nitrous oxide during surgery have suggested no abnormal bleeding during or soon after the operation. It appears, therefore, that in the majority of the patients the degree of platelet dysfunction may not be clinically significant. However, in patients who have mild congenital or acquired platelet disorders the effects of isoflurane and nitrous oxide may be clinically important.

References

1. Gotta AW, Gould P, Sullivan C, Goldiner PL. The effect of enflurane and fentanyl anesthesia on human platelet aggregation in vivo. *Can Anaesth Soc J* 1980;27:319-22.
2. Dalsgaard-Nielsen J, Gormsen J. Effects of halothane on platelet function. *Thromb Haemost* 1980;44:143-5.
3. Ueda I. The effects of volatile general anesthetics on adenosine diphosphate-induced platelet aggregation. *Anesthesiology* 1971;34:405-8.
4. Lichtenfeld KM, Schiffer CA, Helrich M. Platelet aggregation during and after general anesthesia and surgery. *Anesth Analg* 1979;58:293-6.
5. O'Brien JR, Etherington M, Jamieson S. Refractory state of platelet aggregation with major operation. *Lancet* 1971;741-3.
6. Gerrad JM, Duncan PG, Koshyk SA, Glover SM, McCrea JM. Halothane stimulates the aggregation of platelets of both normal individuals and those susceptible to malignant hyperthermia. *Br J Anaesth* 1983;55:1249-57.
7. Kokores JA, Economopoulos TC, Alexopoulos C, Pyrovolakis J, Papayannis AG. Platelet function tests during major operation for gastro-intestinal carcinoma. *Br J Surg* 1977;64:147-9.
8. Qureshi GD, Reinders TP, Swint JJ, Slate MB. Acquired warfarin resistance and weight-reducing diet. *Arch Intern Med* 1981;141:507-9.
9. Fletcher CF, Pearson C, Choi SE, Duma RJ, Evans HJ, Qureshi GD. In vitro comparison of antiplatelet effects of beta-lactam penicillins. *J Lab Clin Med* (In Press).
10. Coller BS, Franza BR, Gralnick HR. The pH dependence of quantitative ristocetin-induced platelet aggregation: theoretical and practical implications—a new device for maintenance of platelet-rich plasma pH. *Blood* 1976;47:841-54.
11. Steel RDG, Torrie JH. Principles and procedures of statistics: a biometrical approach. 2nd ed. New York: McGraw-Hill Book Co, 1980:137-152, 167-170, 580-5.
12. Weiss HJ. Platelet physiology and abnormalities of platelet function. *N Engl J Med* 1975;293:531-41.
13. Shattil SJ, Barrett JS. Platelets and their membrane in hemostasis: physiology and pathophysiology. *Ann Intern Med* 1980;94:108-18.
14. Beck WS, ed. Hematology. Cambridge Massachusetts: MIT Press 1977:524.
15. Born G. Aggregation of blood platelets by adenosine diphosphate and its reversal. *Nature* 1962;194:927-9.
16. O'Brien JR. Platelet aggregation part II. Some results from a new method of study. *J Clin Path* 1962;15:452-5.
17. Mustard JF, Packham MA, Perry DW, Guccione MA, Kinlough-Rathbone RL. Enzyme activities on the platelet surface in relation to the action of adenosine diphosphate. In: *Biochemistry and pharmacology of platelets*. Ciba Foundation Symposium 35. New York: Elsevier-North Holland, 1975.
18. Ginsburg AD. Platelet function in patients with high platelet counts. *Ann Int Med* 1975;82:506-11.
19. Cardamone JM, Edson JR, McArthur JR, Jacob HS. Abnormalities of platelet function in the myeloproliferative disorders. *JAMA* 1972;221:270-3.
20. Cowan DH, Haut M. Platelet function in acute leukemia. *J Lab Clin Med* 1972;79:893-905.

Tourniquet Pain: A Volunteer Study

Rene R. P. M. Hagenouw, MD, Phillip O. Bridenbaugh, MD, Jan van Egmond, PhD, and Roger Stuebing, MS

HAGENOUW RRP, BRIDENBAUGH PO,
VAN EGMOND J, STUEBING R. Tourniquet pain: a
volunteer study. *Anesth Analg* 1986;65:1175-80.

The effect of inflation pressure (300 and 400 mm Hg) and method of exsanguination (gravity and Esmarch bandage) on the time of onset and the severity of tourniquet-induced pain in the lower extremity was investigated in 11 unmedicated adult volunteers. Each volunteer underwent eight experiments in a random order. A visual analog scale was used to assess pain and discomfort. Blood pressure and pulse rate were measured continuously. Experiments were concluded when the pain rose to a prefixed level. All experiments were performed using a standard orthopedic tourniquet (7 cm wide). Ten additional experiments were carried out using a Bier blockade tourniquet (5 cm wide). There were no differences in duration of tourniquet inflation between inflation pressures nor between methods of exsanguination. There was a small and transient but nevertheless

statistically significant increase in blood pressure caused by inflation and a significantly larger increase just before deflation. The 5-cm tourniquet experiments, otherwise identical to the 7-cm tourniquet experiments, were tolerated significantly longer due to a longer time of onset and less severe pain. The 5-cm tourniquet also needed significantly higher inflation pressures to fully occlude the arterial supply (240-450 mm Hg). In all instances, 260 mm Hg was adequate to fully occlude the arterial supply when a 7-cm tourniquet was used. Only half of the experiments were concluded due to intolerable pain at the site of the tourniquet. Most of the others were concluded due to pain mainly in the calf or pain throughout the leg. We conclude that the clinical syndrome of "tourniquet pain" consists of several components and is not due just to the pain and pressure under the tourniquet.

Key Words: PAIN—tourniquet.

Pneumatic tourniquets are widely used to facilitate limb surgery. Reported adverse effects of their use include paralysis (1,2), tendon rupture (3), and fatal pulmonary embolism (4,5). Adverse effects of concern to anesthesiologists also include hypertension during general anesthesia (6,7) and moderate to severe pain during otherwise satisfactory regional anesthesia. This pain, which is promptly relieved by deflation of the tourniquet, can be so severe as to necessitate supplemental general anesthesia.

Though various explanations have been put forward (8-11), little is known about the causes and neural pathways of tourniquet pain. To investigate possible factors influencing the incidence and severity of tourniquet-induced pain, we undertook a study to examine the following: 1) the effect of inflation pressure,

2) the method of exsanguination, and 3) the role of the width of the tourniquet on the intensity and duration of tourniquet pain in healthy, unmedicated, adult volunteers.

Methods

Twelve healthy, unmedicated volunteers each underwent eight experiments in a randomized order. Four experiments were done on each leg, using two pressures (300 mm Hg and 400 mm Hg), and two methods of exsanguination: gravity (by holding the leg up for 2 min) and Esmarch (by wrapping the leg tightly with a rubber bandage). A minimum of 5 days rest was observed between each experiment.

Before the first experiment was carried out, the length of each upper leg (as measured from indentation at the lateral aspect of the knee to the greater trochanter) and the mid-thigh circumference were measured. Age, sex, height, and weight were also noted.

The visual analog scale (VAS) was explained. The VAS used is a line marked linearly from 0 to 10, on which 0 represents no pain or discomfort and 10 stands

Received from the Department of Anesthesia, University of Nijmegen, Nijmegen, The Netherlands and the Department of Anesthesia, University of Cincinnati College of Medicine and the Institute for Policy Research, University of Cincinnati, Cincinnati, Ohio. Accepted for publication May 8, 1986.

Address correspondence to Dr. Bridenbaugh, Department of Anesthesia, University of Cincinnati College of Medicine, Cincinnati, OH 45267-0531.

Table 1. A Typical Experiment Sheet

Date: December 13, 1984					
Running No: 78					
Volunteer No: 2					
Experiment No: 8					
Name:	Age: 34	Height: 174 mm	BP: 136/75 mm Hg		
	Sex: Male	Weight: 70 kg	Pulse: 63/min		
Circumference right thigh:	48 cm	Length of right femur:	43 cm		
Circumference left thigh:	46 cm	Length of left femur:	42 cm		
Right leg Study pressure: 400 mm Hg		Exsanguination: Gravity			
Tourniquet equipment: Stille		Tourniquet width: 7 cm			
Gauge pressure: 120 Atm		Occlusion pressure: 185 mm Hg			
Inflation time: 16:30		Corresponding systolic pressure: 139 mm Hg			
Deflation time: 17:09		Total Tourniquet time: 39 min			
General comments					
Number	Time	BP	Pulse	Pain score	Comments
1	16:28	147/80	64	0	Just before inflation
2	16:31	157/85	69	7	—
3	16:35	162/91	67	3	—
4	16:40	163/92	66	3	Tingling foot-sole
5	16:45	169/89	65	4	Numb foot
6	16:50	149/81	64	4	Numb up to knee
7	16:55	138/84	63	4	Paralysis foot
8	17:00	168/91	66	5	Whole leg hurts
9	17:05	169/99	67	8	Tourniquet hurts most
10	17:09	176/108	72	9	Whole leg hurts
11	17:10	145/84	74	3	Relief, warm leg
12	17:11	168/99	79	8	Tingling, stiffness
13	17:15	166/84	62	1	—

for the worst pain and/or discomfort that the subject can possibly imagine. During the experiments, the volunteer would, if experiencing pain, be asked regularly to rate his or her pain and/or discomfort on this scale. The volunteer was also instructed to try to fix the same degree of pain/discomfort in his or her mind and to conclude all subsequent experiments at that same endpoint. The tourniquet would then be deflated.

The volunteer was placed in a comfortable, half-sitting position out of sight of clocks or monitoring equipment. ECG electrodes were appropriately placed and connected to a combined ECG monitor and digital plethysmograph (Datascope 865CA). A blood pressure cuff was applied and attached to an automatic blood pressure monitor (E.M.E., model 3200). An orthopedic tourniquet was applied to the mid-thigh with one layer of "soft-roll" under wrap. Baseline blood pressure and pulse were measured at a 2-min intervals until stable.

Recent reports (12,13) indicate that the tourniquet pressure needed to fully occlude the arterial blood supply may be significantly greater than the systolic blood pressure. Before the actual experiment was

commenced, the digital plethysmograph was applied to the second toe and the tourniquet slowly inflated until the arterial pulsations disappeared on the oscilloscope (occlusion pressure). Simultaneously, the systolic blood pressure in an upper extremity was measured. These pressures were recorded and the tourniquet deflated.

The leg was then exsanguinated and the tourniquet inflated to the appropriate pressure for that experiment. Pulse and blood pressure were measured 1 min after inflation, followed by measurements at a 5-min interval or sooner if changes in sensation occurred. With each measurement the volunteer was asked to rate his or her pain or discomfort on the VAS and give a verbal description as well. The experiments were continued for 1 hr or until the prefixed degree of pain/discomfort was reached, whichever was sooner, after which the tourniquet was deflated. After deflation, measurements were continued until the VAS value was down to 0-2. Volunteers were not told what the pressure setting was, nor were they told how long the tourniquet had been inflated.

The first 10 experiments were carried out using a

tourniquet with an inflatable width of 5 cm, regularly used for Bier blockades of the upper extremity. It was quickly noted, however, that at 300- and 400-mm Hg inflation pressure, this did not always provide full arterial occlusion. Experiments were therefore also performed using a standard orthopedic tourniquet for the lower extremity with an inflatable width of 7 cm. All experiments, except for the first 10, were carried out using the latter tourniquet. This provided full arterial occlusion at study pressures during all subsequent experiments.

Statistical analysis was performed using the SAS package (SAS Institute, Cary NC). Differences between conditions were analyzed either by analysis of variance or by Student's *t*-test for paired observations. Except as indicated, mean values are given in the text with standard error of the means in parentheses. Statistical significance was assumed when *P* values were below 0.05.

Results

One volunteer discontinued after two experiments due to other commitments. A typical experimental data-sheet is given in Table 1. In general, inflation produced an immediate pain at the site of inflation, which partially subsided to a tolerable level within a few minutes. Ten to 15 minutes after inflation, sensory changes starting at the toes and ascending towards the tourniquet, began and reached the tourniquet approximately 10 min later (20-25 min after inflation). These sensory changes consisted of tingling, numbness, paresthesiae, and sometimes a warm feeling, gradually changing into an ache. This ache got progressively worse. By 20-30 min postinflation, the toes became completely numb and immovable by the subject (paralyzed?). Deflation produced substantial relief for only 30-45 sec, after which a different type of pain returned to a comparable, or even higher VAS score. This pain consisted of severe tingling throughout the leg, a very tight feeling calf, sometimes even cramps, and a buzzing sensation. This pain lasted only a few minutes and was accompanied by vasodilatation and red discoloration of the leg. 'Paralysis' of the toes also disappeared within a few minutes. Figure 1 shows a typical VAS curve. Volunteers were very consistent in their use of the VAS, both for the initial pain levels, as well as the termination pain levels.

Table 2 shows the duration of tourniquet inflation in each type of experiment. There were no significant differences between 300- and 400-mm Hg inflation pressure, nor between gravity and Esmarch exsanguination. The mean overall tourniquet inflation time was 31 ± 10 min. However, VAS values immediately

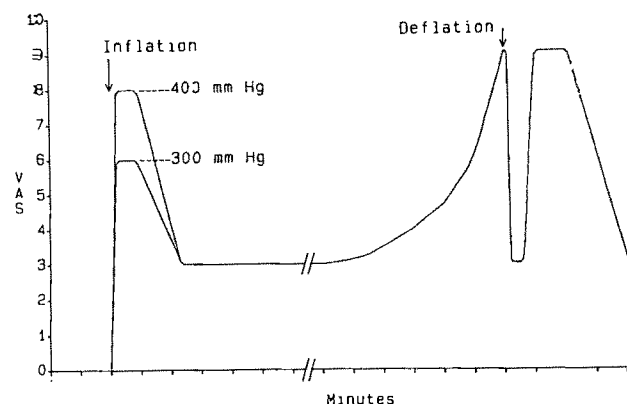


Figure 1. A typical VAS curve. Note the difference in VAS score with inflation to 300 and to 400 mm Hg. After a variable time the pain again increases up to the moment of deflation. Deflation provides only temporary relief, after which the pain, though different in nature, usually peaks about the predeflation VAS value. It then recedes within minutes to about zero.

after inflation to 400 mm Hg were significantly higher than after inflation to 300 mm Hg ($P < 0.0001$).

There was a small, though statistically significant transient increase in systolic blood pressure of 5.0 mm Hg immediately after inflation with a further increase to 9.5 mm Hg above preinflation level just before deflation (Table 3). Both increases and the difference between them were significant ($P < 0.01$). Diastolic blood pressure increased 2.7 mm Hg, with inflation to 300 mm Hg and 8.3 mm Hg, with inflation to 400 mm Hg. The difference was significant ($P < 0.001$). Diastolic blood pressures increased 10.9 mm Hg above preinflation levels just before deflation ($P < 0.001$). Blood pressures returned to pre-inflation levels immediately after deflation. Deflation also resulted in significant 5.5 (1.1) beats/minute increase in pulse rate ($P < 0.001$). In general, the blood pressure followed the same curve as the VAS values in Figure 1.

There was no significant correlation between total tourniquet inflation time and the age, sex, weight, height, control blood pressure, and length or circumference of the thigh.

The 5-cm tourniquet experiments were compared to otherwise identical 7-cm tourniquet experiments. The narrower tourniquet needed occlusion pressures of 240-450 (353) (SD = 69) mm Hg, whereas the wider needed pressures of 145-260 (175) (SD = 23) mm Hg ($P < 0.001$). Volunteers also reported that the wider tourniquet produced more pain. Postinflation VAS values were also significantly higher ($P < 0.002$). The volunteers were able to tolerate the 5-cm tourniquet for a full hour. The difference in tourniquet inflation time was significant ($P < 0.001$).

In only 43 of 88 experiments using the 7-cm tourniquet was deflation because of intolerable pain main

Table 2. Inflation Time in Minutes Related to Type of Experiment

Patient Number	Left Leg				Right Leg			
	Esmarch		Gravity		Esmarch		Gravity	
	300 ^a	400 ^b	300	400	300	400	300	400
1	32	36	37	31	42	37	39	40
2	33	37	37	29	35	39	31	33
3	6	1	21	0	13	18	23	0
4	34	26	32	25	34	31	31	22
5	42	29	45	36	40	40	42	42
6	38	34	35	35	41	1	36	34
7	25	32	39	38	37	30	34	35
8	38	40	36	34	27	39	31	29
9	23	12	31	13	21	27	24	16
10	38	46	38	31	37	33	40	45
11	36	25	40	31	38	29	39	32

^a300, 300 mm Hg tourniquet pressure.^b400, 400 mm Hg tourniquet pressure.

Table 3. Changes in Blood Pressure from Baseline Levels just After Inflation and just before Deflation

	Systolic blood pressure (mm Hg) ^a	Diastolic blood pressure (mm Hg)	
		300 ^b	400 ^c
Baseline before inflation	0	0 ^{e,f}	0 ^{e,f}
Just after inflation	+5.0 (2.8) ^d	+2.7 (2.4) ^e	+8.3 (2.4) ^e
Just before deflation	+9.5 (2.8) ^d	+10.9 (1.7) ^f	+10.9 (1.7) ^f

^aValues in parentheses are SEM.^b300, 300 mm Hg tourniquet pressure.^c400, 400 mm Hg tourniquet pressure.^d*P* < 0.01 compared to baseline.^e*P* < 0.05 compared to baseline.^f*P* < 0.001 compared to baseline.

at the tourniquet site. In 21 experiments, the reason for deflation was pain in the calf, and in 13 cases, the whole leg hurt from tourniquet to toes. The remaining experiments were terminated because of pain at the knee, the back of the leg, the foot, or due to extremely painful spasms in the thigh (Table 4). In a few cases, radiation of the pain into the groin was reported.

Discussion

Contrary to what one would expect, a comparison of 300- and 400- mm Hg inflation pressures resulted in no significant difference in the time it took before the pain from a thigh tourniquet became unbearable. Subjectively, however, the volunteers were quite able to tell the difference. Current orthopedic practice relies upon tourniquet inflation pressures ranging from 100 mm Hg above the systolic blood pressure to up to 600 mm.Hg. Using a tourniquet with an inflatable width of 7 cm, 350 mm Hg of inflation pressure should suffice for all normotensive patients. A higher tourniquet pressure in a normal subject will not provide more

occlusion, but may well cause more damage to the limb (1).

Volunteers in this study were neither medicated nor anesthetized and were able to tolerate the inflated tourniquet for a mean 31 ± 10 min. One would expect that addition of premedication plus spinal, epidural, or general anesthesia would either eliminate this phenomenon completely or significantly delay its onset. Tourniquet-induced pain during spinal or epidural anesthesia has been noted to occur 60–90 min after inflation of the tourniquet. It has also been reported that tourniquet inflation for more than 1 hr results in a high incidence of hypertension (6,7). In a recent study (14) of patients receiving spinal anesthesia using a similar VAS pain score, the mean time for onset of tourniquet pain to similar pain scores was 73 min. Whereas all volunteers experienced similar degrees and durations of tourniquet pain, only a small percent of anesthetized patients experienced this phenomenon. It is clear therefore that anesthesia does reduce the incidence and delay the onset of tourniquet pain beyond the 31 min noted here. Of interest, however,

Table 4. Reasons for Tourniquet Deflation

Patient number	Left leg				Right leg			
	Esmarch		Gravity		Esmarch		Gravity	
	300	400	300	400	300	400	300	400
1	T	C	C	K	C	?	C	C
2	W	C	W	T	T	W	W	W
3	S	T	T	T	F	F	T	T
4	T	T	T	T	T	T	F	S
5	C	C	C	?	C	C	C	C
6	T	T	C	T	T	T	T	W
7	T	T	T	T	T	T	W	T
8	T	T	T	T	T	T	T	T
9	T	T	C	?	T	C	W	T
10	C	C	C	W	W	W	C	C
11	B	W	T	W	T	B	T	T

Abbreviations: T, tourniquet hurts most (43); C, Calf hurts most (21); W, whole leg hurts (13); F, Foot hurts most (3); B, Back of leg hurts most (2); S, Painful thigh spasms (2).

is the fact that unmedicated volunteers can tolerate the tourniquet for such a long period of time.

An unexpected result was the difference between the use of a 5-cm upper arm tourniquet compared to a standard 7-cm orthopedic tourniquet. Clearly the latter, though causing more pain, is preferable due to the greatly reduced occlusion pressure. The required lower inflation pressure may lead to a lower incidence of pressure-related adverse effects, such as compression trauma of the sciatic nerve (15).

Tourniquet pain experiments have been and still are used to assess the efficacy of analgesics using a model such as that of Smith et al. (16,17). In this model, muscular exercise is performed to enhance limb ischemia and acidosis due to anaerobic muscle metabolism. The model of Smith et al. differs from the model reported here where the volunteers were told not to move their leg during the experiments. The observation in this study that the pain in the thigh and the calf subsides almost immediately after deflation argues against the assumption that tourniquet pain is caused by tissue ischemia. It is unlikely that all anaerobic metabolic products are washed away within 10 sec. It is therefore not necessarily acidosis and/or ischemia in the limb that caused the most pain. Furthermore, no "tourniquet-like" pain is reported in patients having peripheral vascular surgery under spinal anesthesia during surgical clamping of the arterial supply. The referred nature of at least part of tourniquet pain would seem to point to a direct effect on the nerve trunk. Another possible explanation is that the main pain arises from the sensory innervations of the vascular bed, which do not follow the dermatomal pattern. Clearly, the arteries are one of the first structures to have their anaerobic products

washed away. The delayed postdeflation burning and tingling pain seems to be related to the reperfusion of tissues and the washing away of intracellularly accumulated anaerobic metabolic products (18). Yet another indication that tourniquet pain is not significantly due to vascular ischemia is the fact that there are no reports of such a pain phenomenon during vascular surgery after aortic or major arterial cross clamping. Similar pain sensations have been reported, however, by patients experiencing acute arterial occlusion to the lower extremity.

Finally, the fact that only half the experiments were terminated due to intolerable pain at the site of the tourniquet may well mean that the true incidence of tourniquet-induced pain during otherwise satisfactory regional anesthesia is higher than generally thought. The results of this study indicate that discomfort or pain anywhere in the leg may be tourniquet-induced.

References

1. Bolton CF, McFarlane RM. Human pneumatic tourniquet paralysis. *Neurology* 1978;28:787-93.
2. Cobuer JJ, Nitz AJ. Postmeniscectomy tourniquet palsy and functional sequelae. *Am J Sports Med* 1982;10:211-4.
3. Logel RJ. Rupture of the long tendon of the biceps brachii muscle. An unusual case related to use of the pneumatic tourniquet. *Clin Orthop* 1976;121:217-21.
4. San Juan AC, Stanley TH. Pulmonary embolism after tourniquet inflation. *Anesth Analg* 1984;63:374.
5. Follard BJ, Lovelock HA, Jones RM. Fatal pulmonary embolism secondary to limb exsanguination. *Anesthesiology* 1983;58:373-4.
6. Kaufman RD, Walts LF. Tourniquet induced hypertension. *Br J Anaesth* 1982;54:333-6.
7. Valli H, Rosenberg PH. Effects of three anaesthesia methods on haemodynamic responses connected with the use of thigh

- tourniquet in orthopaedic patients. *Acta Anaesthesiol Scand* 1985;29:142-7.
8. Cole F. Tourniquet pain. *Anesth Analg* 1952;31:63-4.
 9. Egbert LD, Deas TC. Cause of pain from a pneumatic tourniquet during spinal anesthesia. *Anesthesiology* 1962;23:287-90.
 10. de Jong RH. Tourniquet pain during spinal anesthesia. *Anesthesiology* 1962;23:881-2.
 11. de Jong RH, Cullen SC. Theoretical aspects of pain: bizarre pain phenomena during low spinal anesthesia. *Anesthesiology* 1963;24:628-35.
 12. Davies JAH, Hall ID, Wilkey AD, Smith JE, Walford AJ, Kale VR. Intravenous regional analgesia. The danger of the congested arm and the value of occlusion pressure. *Anaesthesia* 1983;39:416-21.
 13. Ogden PN. Failure of intravenous regional analgesia using a double cuff tourniquet. *Anaesthesia* 1984;39:456-9.
 14. Bridenbaugh PO, Hagenouw RRP, Gielen MJ, Edstrom HH. Addition of glucose to bupivacaine in spinal anesthesia increases incidence of tourniquet pain. *Anesth Analg* 1986;65:1181-5.
 15. Fowler TJ, Danta G, Gilliat RW. Recovery of nerve conduction after a pneumatic tourniquet: observations on the hind-limb of the baboon. *J Neurol Neurosurg Psychiatry* 1972;35:638-47.
 16. Smith GM, Egbert LD, Markowitz RA, Mosteller F, Beecher HK. An experimental pain method sensitive to morphine in man: the submaximum effort tourniquet technique. *J Pharmacol Exp Ther* 1966;154:324-32.
 17. Smith GM, Lowenstein E, Hubbard JH, Beecher HK. Experimental pain produced by the submaximum effort tourniquet technique: further evidence of validity. *J Pharmacol Exp Ther* 1968;163:468-74.
 18. Ochoa JL, Torebjörk HE. Paraesthesiae from ectopic impulse generation in human sensory nerves. *Brain* 1980;103:835-53.

Addition of Glucose to Bupivacaine in Spinal Anesthesia Increases Incidence of Tourniquet Pain

Phillip O. Bridenbaugh, MD, Rene R. P. M. Hagenouw, MD, Mathieu J. M. Gielen, MD, and Håkan H. Edström, PhD

BRIDENBAUGH PO, HAGENOUW RRP, M, GIELEN MJM, EDSTROM HH. Addition of glucose to bupivacaine in spinal anesthesia increases incidence of tourniquet pain. *Anesth Analg* 1986;65:1181-5.

The effect of baricity of 0.5% bupivacaine on the incidence of tourniquet pain when used for spinal anesthesia was evaluated in 60 patients undergoing orthopedic surgery. Three ml of either hyperbaric (8% glucose) or isobaric (glucose-free) solution was used. A standard 7-cm orthopedic

tourniquet was applied at the thigh and was inflated to 300 mm Hg for 2 hr or until the patient experienced pain from the tourniquet. During application time, the levels of sensory block to pin prick were similar in the groups. The incidence of tourniquet pain in the glucose-free group (4/30) was significantly lower than in the hyperbaric group (11/30).

Key Words: ANESTHETIC TECHNIQUES, SPINAL—tourniquet pain. PAIN—tourniquet.

The widespread use of pneumatic tourniquets in limb surgery has been accompanied by reports on adverse effects, including paralysis (1-6), tendon rupture (7), arterial complications (8,9), and even fatal pulmonary embolism (10). Other effects of concern to anesthesiologists are hypertension and tachycardia during general anesthesia (11,12) and moderate to severe pain from the tourniquet during otherwise satisfactory regional anesthesia. This pain, which is promptly relieved by deflation of the tourniquet, can be so severe as to necessitate supplemental general anesthesia.

Though various explanations have been offered (13-16), the mechanism of tourniquet pain is unclear. Differences between drug dosages (14) or between drugs (17) have been suggested. The aim of the present study was to compare in a randomized double blind study 3 ml 0.5% glucose-free bupivacaine (isobaric) with 3 ml 0.5% bupivacaine in 8% glucose (hyperbaric) regarding the incidence of tourniquet induced pain of the lower extremity.

Materials and Methods

Sixty patients (30 men) aged 18-75 yr, undergoing orthopedic surgery of the lower limb under spinal

anesthesia were studied. The study was approved by the Human Research Advisory Committee of the University Hospital, Nijmegen. Informed consent was obtained from all patients prior to their inclusion in the study.

Most patients were given oral diazepam, 10 mg (one was given oxazepam, 20 mg), 1-2 hr before the lumbar puncture. After an intravenous infusion was established and vital signs monitored, the patient was placed in the sitting position and lumbar puncture was performed with a 25- or 22-gauge needle at the L2-3, L3-4, or L4-5 interspace using a midline or paramedian (seven patients) approach.

The patients were randomly allocated to receive 3 ml of 0.5% bupivacaine, either glucose-free or containing 8% glucose. Once a free flow of cerebrospinal fluid was obtained, the study solution was injected at a rate of 0.2 ml/sec (without barbotage), the needle withdrawn, and the patient immediately turned supine.

The cephalad and caudad spread of sensory blockade, the degree of motor blockade of the lower limbs, the blood pressure (by an automatically inflated cuff), and the heart rate (by electrocardiogram) were monitored during anesthesia. The levels of sensory blockade were assessed using a blunt needle. The degree of motor blockade was assessed on a 0-3 scale as previously described (18).

Approximately 30 min after injection of the spinal drug, surgical preparation commenced with exsanguination of the extremity and application of a layer of "soft-roll" underwrap prior to placement of a standard 7-cm orthopedic tourniquet at the mid-thigh level.

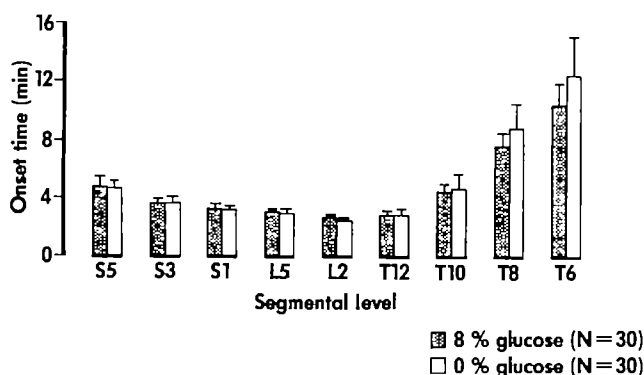
Received from the Department of Anaesthesia, University of Nijmegen, Nijmegen, The Netherlands, and the Department of Anesthesia, University of Cincinnati College of Medicine, Cincinnati, Ohio, USA. Accepted for publication May 12, 1986.

Address correspondence to Dr. Bridenbaugh, Department of Anesthesia, University of Cincinnati College of Medicine, Cincinnati, OH 45267-0531.

Table 1. Patient Characteristics (mean \pm SEM)

Group	Age	Height (cm)	Weight (kg)	Sex
Glucose-free	39 \pm 15	172 \pm 10	71 \pm 12	13 F/17 M
Hyperbaric	42 \pm 19	171 \pm 10	72 \pm 13	17 F/13 M

F, female; M, male.

Figure 1. Time of onset of analgesia to different segmental levels (mean \pm SEM).

The tourniquet was then inflated to 300 mm and remained inflated for either 2 hr or until intolerable to the patient, whichever came first. If the patient experienced pain thought to be related to the tourniquet, a standard visual analog scale (VAS) which ranges from 0 to 10, was explained to the patient and used to assess the degree of pain from the tourniquet. In case of a high or rapidly rising value on the VAS, the tourniquet was deflated. If the pain subsided or decreased substantially within 1 min after deflation of the tourniquet, the pain was considered to be of tourniquet origin.

The results obtained in the groups were analyzed statistically using Wilcoxon test or Fischer-Irwin test where appropriate. A *P* value less than 0.05 was considered statistically significant.

Results

There were no statistically significant differences between the patients in the two groups in relation to age, weight, height or sex (Table 1). The mean onset time for analgesia to the T10 level was similar for each solution (Fig. 1). The mean time until the spread of analgesia was maximal was approximately 20 min for each solution. The mean maximum spread of analgesia was to T4-5 for each solution, and the levels of analgesia were similar up to 3 hr after administration of the local anesthetic solutions (Fig. 2). The duration of analgesia in the lumbar/sacral segments was sta-

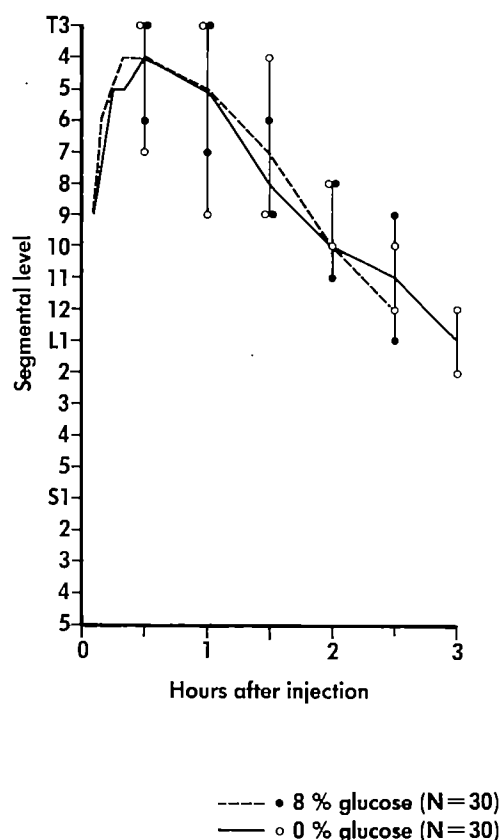


Figure 2. Segmental spread of analgesia (median values, lower/upper bounds at 95% confidence level).

tistically significantly longer ($P < 0.01$) with the glucose-free solution than that obtained with the hyperbaric solution (Fig. 3).

No difference was found between the solutions with regard to rapidity of onset of motor blockade. Duration of complete motor blockade was statistically significantly greater ($P < 0.001$) for the glucose-free solution (158 min) than for the hyperbaric solution (109 min). Twenty-six patients in the glucose-free group (87%) and 24 patients in the hyperbaric group (80%) had complete, i.e., degree 3, motor blockade.

Average operative time was 24 ± 15 min in the glucose-free group and 25 ± 8 min in the hyperbaric group and was similar for the two groups. Surgical analgesia was satisfactory for all but one patient in each group.

The median duration of inflation of the tourniquet was 120 min in the glucose-free group and 99 min in the hyperbaric group. The levels of analgesia at time of deflation of the tourniquet are shown in Figure 4. The median upper level was T9 in the hyperbaric and T10-11 in the glucose-free groups (cf. Fig. 2). In at least five patients in the hyperbaric group and in one patient in the glucose-free group, regression of an-

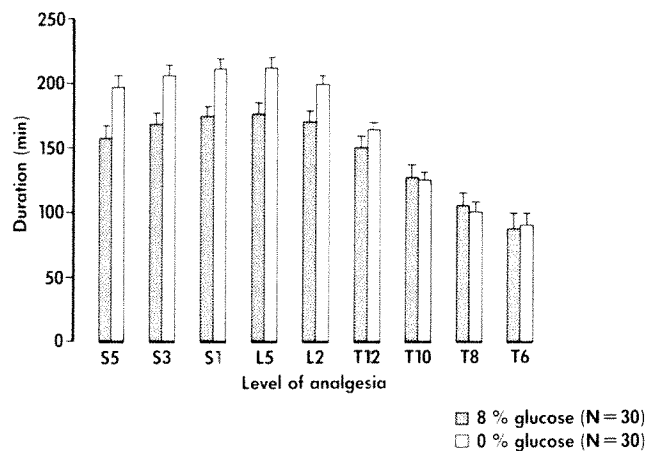


Figure 3. Duration of analgesia at different segmental levels (mean \pm SEM).

algnesia upwards from S5 was observed when tourniquet pain was experienced, i.e., in all patients but one in whom sacral regression of analgesia was recorded, tourniquet pain was experienced (Table 2).

Pain from the tourniquet during the 2-hr inflation time was experienced in four patients in the glucose-free group and in 11 patients in the hyperbaric group ($P < 0.05$). The degree of tourniquet pain based on the VAS scale at the time of deflation of the tourniquet varied in the hyperbaric group from 3 to 9 (Md 4.5) and in the glucose-free group 1, 3.5 and 3.5 (Table 2); it was thus not possible to evaluate any possible differences between the groups with regard to descriptions of pain.

No changes in blood pressure or pulse could be specifically attributed to the onset of tourniquet pain. Changes in blood pressure and/or pulse requiring treatment with ephedrine and/or atropine occurred in only seven patients at the beginning of the case (Fig. 5). One patient in each group experienced nausea, and three patients (all in the glucose-free group) had post-spinal headache.

Discussion

The present study shows that during the 2 hr the tourniquet was inflated, the proximal level of sensory block to pin prick was similar for the two solutions. In spite of this, the incidence of tourniquet pain was different in the groups using the same dose and volume of bupivacaine. This raises the question whether glucose has some effect on the perception or transmission of tourniquet pain.

Tourniquet pain did not seem to be related in this study to the cephalad segmental level of cutaneous

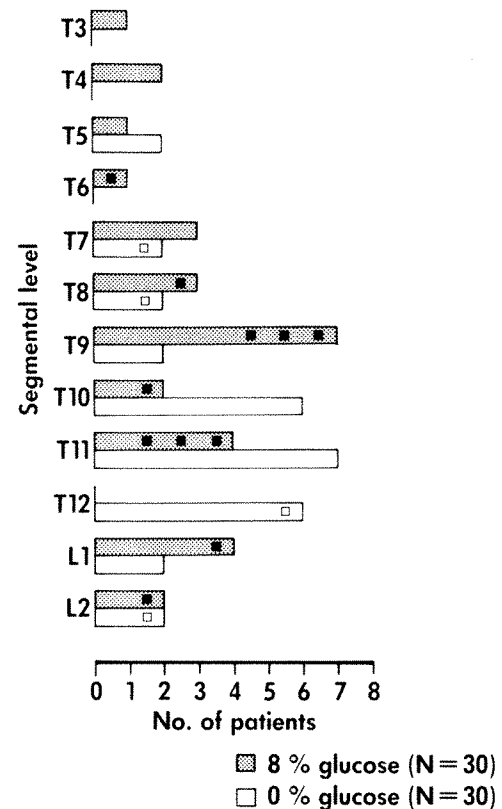


Figure 4. Levels of analgesia and numbers of patients at that level when tourniquet was deflated. Each small square represents patient with tourniquet pain requiring tourniquet deflation and sensory level at that time.

analgesia to pin prick, which is in accordance with other authors (16,18). Most of the patients in this study with pain from the tourniquet had levels of analgesia in the mid or lower thoracic region. Conversely, some patients did not experience pain from the tourniquet in spite of upper levels of analgesia as low as the lumbar region. Nor did we find any consistency in the time of occurrence of tourniquet pain after administration of the local anesthetic. This is in accordance with data from Rocco et al. (17-19).

Strichartz and Zimmermann (20) theorized that the ability of a tourniquet to produce pain arises from selective transmission by the small A- δ and C-fibers, which are being repetitively stimulated by the tourniquet, and whose postsynaptic effect in the dorsal horn cannot then be inhibited by impulses in the totally blocked large fibers. It has also been reported that after a period of repetitive activity, a single compound C potential is greater in amplitude than in the resting nerve (21).

Strichartz and Zimmermann (20), using de-sheathed cat sural nerve marginally blocked with low lidocaine concentrations (0.1-0.5 mM), found that

Table 2. Levels of Analgesia (Pin Prick) and Degree of Tourniquet Pain at Time of Deflation of the Tourniquet

Glucose-free group				Hyperbaric group			
Patient	Min after application of tourniquet	Level of analgesia	VAS	Patient	Min after application of tourniquet	Level of analgesia	VAS
1	117	T12-L4	3.5	5	103	T11-S3	4.5
2	8	T8-S5	1	6	44	L1-S5	7
3	— ^a	T7-S5	— ^b	7	91	~L1-L5	4
4	139	L2-S5	3.5	8	89	~T9-S5	3
				9	76	T11-S5	6
				10	55	~L2-S4/5	7
				11	47	T9-S5	9
				12	41	T9-S5	7
				13	71	~T6-S5	4
				14	90	T10-S3/4	3
				15	49	T8-S4/5	4

^aPatient was given general anesthesia during surgery but had pain from the tourniquet after awakening, approximately 2 hr after injection.

^bNot assessed.

VAS, visual analog scale.

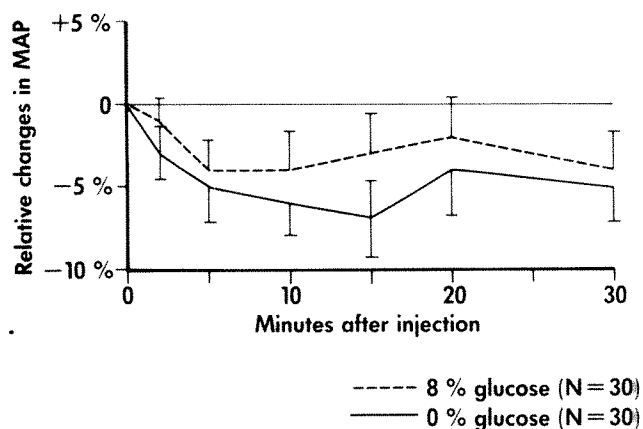


Figure 5. Changes in mean arterial pressure during the first 30 min after injection (mean \pm SEM).

during repetitive stimulation, the action potential of the large A- β fibers decreased more than the decrease seen during single shocks. On the other hand, the reduced action potentials from A- δ and, particularly, C-fibers increased during repetitive stimulation at 5–10 Hz. Higher stimulus frequencies and lidocaine concentrations abolished this effect. Consequently, with a "marginal" block present, which might be the case when the hyperbaric bupivacaine solution is used, the blockade of the small fibers may decrease during repetitive stimulation from a tourniquet.

It is difficult to relate any of the foregoing theory of the mechanism of tourniquet pain to the observations of this study that more patients who received hyperbaric spinal anesthesia experienced tourniquet pain than did the patients who received glucose free

(isobaric) spinal anesthesia. Since the total duration of both motor and sensory blockade far exceeded the 120-min period of tourniquet inflation, one has difficulty implying that differences in the rates of regression between the two groups account for the observations.

There is little in the clinical literature to support differences in sensory and motor blockade between hyperbaric and isobaric spinal solutions. Nor is there evidence that somatic sensory or motor blockade has any bearing on occurrence of tourniquet pain. Although we can postulate tourniquet pain is "visceral" in type or mediated via C-fiber pathways, we have little data relating the effect of hyperbaric solutions on C-fiber conduction. Unpublished studies by Fink showed a 2–3 fold reduction in lidocaine blockade of C-fibers (rabbit vagus nerve) when the perfusate was changed from an electrolyte solution to a sucrose solution. Studies to confirm the effects of osmolality on spinal anesthesia in primates revealed a longer sensory and motor block with hyperbaric solutions (22).

A number of previous clinical trials have compared isobaric and hyperbaric spinal solutions by varying the position of the patient during injection of the drug (sitting vs lateral) and also by varying the time patients remained in the sitting position after injection. Because glucose-free bupivacaine is slightly hyperbaric, patients who remain sitting for 2 min after injection of glucose-free bupivacaine had higher sensory levels than patients receiving hyperbaric solutions (23–27). In spite of the fact that posture may have a slight effect on duration of spinal anesthesia, as did baricity, the fact remains that at the time tourniquet pain occurs, sensory levels are still high enough so

that one cannot incriminate descending levels of sensory analgesia as the causative factor (Fig. 3).

It is conceivable, because we did note regression of sacral analgesia in some patients with tourniquet pain, that a certain intensity of quality of sacral blockade is necessary to block noxious impulses from the tourniquet. In an additional study of tourniquet pain in volunteers (published in this issue) (28), the intensity of pain seemed as much due to ischemia of the entire leg as it did from pressure of the tourniquet itself. Conceivably then, we have a situation of increasing noxious impulses traveling over neural pathways in which the level of blockade is decreasing. Future studies may need to pay closer attention to the intensity and duration of blockade of the lower lumbar and sacral segments (S-1?) and relate those variables to the occurrence of tourniquet pain.

References

1. Bolton CF, McFarlane RM. Human pneumatic tourniquet paralysis. *Neurology* 1978;28:787-93.
2. Garland DE, Hughston JC. Peroneal nerve paralysis: a complication of extensor reconstruction of the knee. *Clin Orthop* 1979;140:169-71.
3. Weingarden SI, Louis DL, Waylonis GW. Electromyographic changes in postmeniscectomy patients. *JAMA* 1979;241:1248-50.
4. Dobner JJ, Nitz AJ. Postmeniscectomy tourniquet palsy and functional sequelae. *Am J Sports Med* 1982;10:211-4.
5. Aho K, Sainio K, Kianta M, Varpanen E. Pneumatic tourniquet paralysis (case report). *J Bone Joint Surg* 1983;65B:441-3.
6. Mukherjee DJ. Tourniquet paralysis. *J Indian Med Assoc* 1977;69:130-2.
7. Logel RJ. Rupture of the long tendon of the biceps brachii muscle. An unusual case related to use of the pneumatic tourniquet. *Clin Orthop* 1976;121:217-21.
8. Giannestras NJ, Cranley JJ, Leutz M. Occlusion of the tibial artery after a foot operation under tourniquet. *J Bone Joint Surg* 1977;59A:682-3.
9. McAuley CE, Steed DL, Webster MW. Arterial complications of total knee replacement. *Arch Surg* 1984;119:960-2.
10. San Juan AC, Stanley TH. Pulmonary embolism after tourniquet inflation. *Anesth Analg* 1984;63:374.
11. Kaufman RD, Walts LF. Tourniquet-induced hypertension. *Br J Anaesth* 1982;54:333-6.
12. Valli H, Rosenberg PH. Effects of three anaesthesia models on haemodynamic responses connected with the use of thigh tourniquet in orthopaedic patients. *Acta Anaesthesiol Scand* 1985;29:142-7.
13. Cole F. Tourniquet pain. *Anesth Analg* 1952;31:63-4.
14. Egbert LD, Deas TC. Cause of pain from a pneumatic tourniquet during spinal anesthesia. *Anesthesiology* 1962;23:287-90.
15. de Jong RH. Tourniquet pain during spinal anesthesia. *Anesthesiology* 1962;23:881-2.
16. de Jong RH, Cullen SC. Theoretical aspects of pain: bizarre pain phenomena during low spinal anesthesia. *Anesthesiology* 1963;24:628-35.
17. Rocco AG, Concepcion M, Sheskey MC, Murray E, Edstrom H, Covino BG. A double blind evaluation of intrathecal bupivacaine without glucose and a standard solution of hyperbaric tetracaine. *Reg Anesth* 1984;9:1-7.
18. Sheskey MC, Rocco AG, Bizzarri-Schmid M, Francis DM, Edstrom H, Covino BG. A dose response study of bupivacaine for spinal anesthesia. *Anesth Analg* 1983;62:931-5.
19. Rocco AG, Raymond SA, Murray E, Dingra U, Freiburger D. Differential spread of blockade of touch, cold, and pinprick during spinal anesthesia. *Anesth Analg* 1985;64:917-23.
20. Strichartz G, Zimmermann M. An explanation for pain originating from tourniquets during regional anesthesia. *Reg Anesth* 1984;9:44-5.
21. Douglas WW, Ritchie JM. Mammalian nonmyelinated nerve fibers. *Physiol Rev* 1962;42:297-334.
22. Denson DD, Bridenbaugh PO, Turner PA, Phero JC. Comparison of neural blockade and pharmacokinetics after subarachnoid lidocaine in the Rhesus monkey. II: Effects of volume, osmolality and baricity. *Anesth Analg* 1983;62:995-1001.
23. Cummings GC, Bamber DB, Edstrom HH, Rubin AP. Subarachnoid blockade with bupivacaine. A comparison with cinchocaine. *Br J Anaesth* 1984;56:573-9.
24. Chambers WA, Edstrom HH, Scott DB. Effect of baricity on spinal anaesthesia with bupivacaine. *Br J Anaesth* 1981;53:279-82.
25. Kruger D, Iphie P, Nolte H, Edstrom H. Effekt der Glukosekonzentration auf Spinalanaesthesien mit Bupivacain 0.5%. *Reg Anaesth* 1983;6:1-3.
26. Gielen MJM, DeGrood PMRM, Edstrom HH, Crul JF. Comparison of bupivacaine and tetracaine for spinal anesthesia. *Reg Anaesth* 1984;9:62-7.
27. Bengtsson M, Edstrom HH, Lofstrom JB. Spinal analgesia with bupivacaine, mepivacaine, and tetracaine. *Acta Anaesthesiol Scand* 1983;27:278-83.
28. Hagenouw RRPM, Bridenbaugh PO, van Egmond J, Stuebing R. Tourniquet pain: a volunteer study. *Anesth Analg* 1986;65:1171-80.

Effect of Short-term Smoking Halt on Carboxyhemoglobin Levels and P_{50} Values

J. Reddy Kambam, MD, Lily H. Chen, MD, and Steve A. Hyman, MD

KAMBAM JR, CHEN LH, HYMAN SA. Effect of short-term smoking halt on carboxyhemoglobin levels and P_{50} values. *Anesth Analg* 1986;65:1186-8.

Fifteen informed volunteers who smoked one to two packs of cigarettes per day were studied to measure changes in carboxyhemoglobin levels and P_{50} after smoking was stopped for 12 hr. Before smoking was stopped, carboxyhemoglobin levels ($6.55 \pm 0.40\%$) were above normal, and the P_{50} (22.92 ± 0.25 mm Hg) was significantly shifted to the left.

After smoking was stopped for 12 hr there was a significant decrease in carboxyhemoglobin levels to $1.06 \pm 0.16\%$ ($P < 0.001$), and P_{50} shifted towards normal to 26.41 ± 0.14 mm Hg ($P < 0.001$). The authors conclude that within even as little as 12 hr after cessation of smoking, carboxyhemoglobin and P_{50} levels change towards normal values.

Key Words: OXYGEN, OXYHEMOGLOBIN DISSOCIATION— P_{50} . BLOOD, HEMOGLOBIN—oxygenation. COMPLICATIONS—smoking.

Cigarette smoking is associated with increased levels of carboxyhemoglobin in the blood (1). There is evidence that carboxyhemoglobin shifts the oxyhemoglobin dissociation curve to the left (2). Several investigators have reported the effects of cessation of smoking for short as well as longer duration on pulmonary and cardiovascular systems. The purpose of the present study was to investigate the effect of cessation of smoking for 12 hr on carboxyhemoglobin levels and on the oxyhemoglobin dissociation curve.

Methods

Fifteen informed healthy volunteers (8 men, 7 women, aged 24–50 yr) who smoked one to two packs of cigarettes per day for more than a year were included in this study. With the approval of the Committee for the Protection of Human Subjects, 5 ml of venous blood was drawn into a heparinized syringe from each subject. 50 μ l of this blood was used to measure the carboxyhemoglobin concentration by using a deoxygenation capillary tube and a Radiometer, OSM2 Hemoximeter®. The remaining blood sample was divided into two aliquots (alliquot A and alliquot B) and equilibrated with known humidified gases in an

IL 237 Tonometer for 15 min at 37°C. The alliquot A blood sample was equilibrated with 3.5% oxygen, 5.6% carbon dioxide, and the balance nitrogen. The alliquot B blood sample was equilibrated with 4% oxygen, 5.6% carbon dioxide, and the balance nitrogen. At the end of each equilibration, total hemoglobin and percent oxygen saturation of the hemoglobin were measured in a Radiometer, OSM2 Hemoximeter®. Simultaneously, blood gas tensions were measured in a Corning 168 pH/blood gas analyzer. All patients were asked to stop smoking for 12 hr (8 PM to 8 AM), and the above procedure was repeated and data collected. The Radiometer, OSM2 Hemoximeter®, and pH, PCO_2 , and PO_2 electrodes of Corning 168 pH/blood gas analyzer were calibrated before and after each determination of the blood samples. Barometric pressure adjustments were also made in the blood gas machine. The measured PO_2 data were corrected to pH 7.40. Because the uniform carbon dioxide in the gas mixtures gave a normal PCO_2 of 40 mm Hg and the blood gas measurements were done at 37°C, no PCO_2 or temperature corrections were needed. A two-point saturation curve was plotted in the linear portion of the oxyhemoglobin dissociation curve, and P_{50} was obtained from the saturation curve for both control and fasting samples (Fig. 1). Data were analyzed for statistical significance utilizing Student's paired *t*-test.

Results

Table 1 contains the values of total hemoglobin, carboxyhemoglobin, and P_{50} of blood samples collected

Studies completed at Vanderbilt University Hospital, Nashville, Tennessee. Presented at the Annual Meeting of the American Society of Anesthesiologists, Las Vegas, October, 1982.

Received from the Department of Anesthesiology Vanderbilt University Medical Center, Nashville, Tennessee. Accepted for publication June 3, 1986.

Address correspondence to Dr. Kambam, Department of Anesthesiology, Vanderbilt University Hospital, Nashville, TN 37232.

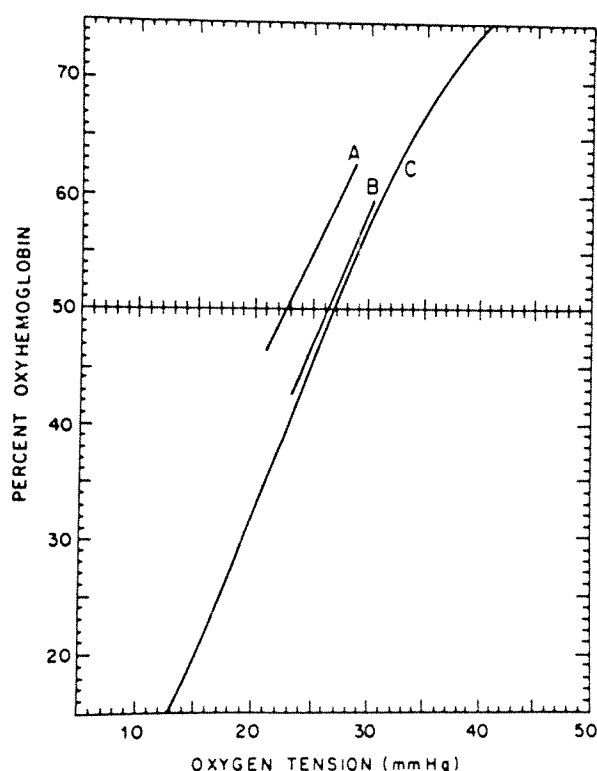


Figure 1. Effect of smoking on the P_{50} : curve A, before smoking was stopped ($P_{50} = 22.92$ mm Hg); curve B, after smoking was stopped for 12 hr ($P_{50} = 26.41$ mm Hg); curve C, normal nonsmoker ($P_{50} = 27$ mm Hg). Only steep portions of oxyhemoglobin dissociation curves (OHDC) were shown for curves A and B. Curve C is the standard OHDC.

before and after smoking was stopped for 12 hr. The P_{50} and carboxyhemoglobin values while smoking were 22.92 ± 0.25 mm Hg and $6.55 \pm 0.40\%$, respectively. After smoking was stopped for 12 hr, carboxyhemoglobin levels decreased to $1.06 \pm 0.16\%$ ($P < 0.001$), and P_{50} shifted towards normal to 26.41 ± 0.14 mm Hg ($P < 0.001$).

Discussion

The relationship between PO_2 and percentage saturation of hemoglobin with oxygen is expressed as the oxyhemoglobin dissociation curve. P_{50} is the partial pressure of oxygen at which 50 percent of hemoglobin is oxyhemoglobin at a pH of 7.4, PCO_2 of 40 mm Hg, and temperature of 37°C . The volume of oxygen that can be unloaded to the tissues at any given PO_2 is increased with a higher P_{50} (shift to the right) and decreased with a lower P_{50} (shift to the left).

Smoking is a major risk factor associated with perioperative respiratory and cardiovascular complications (3-10). Evidence also suggests that cigarette smoking causes imbalance in the prostaglandins and

Table 1. Total Hemoglobin (Hgb), Carboxyhemoglobin (COHgb), and P_{50} Values before and after Stopping Smoking for 12 hr

	Before Stopping		After Stopping		P
	Mean	SEM	Mean	SEM	
Hgb (g/dl)	15.74	0.14	15.56	0.15	ns
COHgb (%)	6.55	0.40	1.06	0.16	$< 0.001^a$
P_{50} (mm Hg)	22.92	0.25	26.41	0.14	$< 0.001^a$

P values obtained by Student's *t*-test for paired data; ns, not significant. $n = 15$ each.

^aSignificance of difference between paired data.

promotes vasoconstriction and excessive platelet aggregation (11-15). Two of the constituents of cigarette smoke, nicotine and carbon monoxide, have adverse cardiovascular effects (16,17). Carbon monoxide increases the incidence of arrhythmias and has a negative inotropic effect both in animals and humans (17-20). Smoking causes an increase in carboxyhemoglobin levels, resulting in a leftward shift in P_{50} , which appears to represent a risk factor for some of these cardiovascular complications. There are two mechanisms responsible for the leftward shift of oxyhemoglobin dissociation curve when carbon monoxide is present in the blood (2). Carbon monoxide has a direct effect on oxyhemoglobin, causing a leftward shift of the oxygen dissociation curve, and carbon monoxide also reduces the formation of 2,3-DPG by inhibiting glycolysis in the erythrocyte. Nicotine, on the other hand, has a stimulatory effect on the autonomic nervous system (17,21-24). The effects of nicotine on the cardiovascular system last less than 30 min (20,21).

The beneficial effects of cessation of smoking for short as well as longer periods on respiratory and cardiovascular systems have been investigated. Investigators found that it requires several weeks before any improvement in lung function tests is seen (24,25). Abstinence from smoking for a short period is beneficial to the cardiovascular system (26-28), probably the result of a decrease in carboxyhemoglobin levels and return of the oxyhemoglobin dissociation curve towards normal, as we have shown in this present study. Stopping smoking for prolonged periods has also proven advantageous to the cardiovascular system as the hematocrit and blood viscosity start to decrease, often within days (29).

Major shifts in oxygen dissociation have little effect on arterial oxygen saturation when PaO_2 is in the normal range of 80-100 mm Hg. If oxygen consumption is constant, a rightward shift causes an increase in venous oxygen tension (PvO_2) and a leftward shift is accompanied by a decrease in PvO_2 . A decrease in PvO_2 is observed in the presence of carboxyhemoglo-

bin (30). Decline in PvO_2 below a certain critical level is believed to cause tissue hypoxia (31). Because oxyhemoglobin dissociation returns to normal with cessation of smoking for 12 hr, one would also expect the PvO_2 to return to normal after 12 hr of abstinence from smoking. Our preliminary observations suggest that this is so. Bank blood collected from chronic smokers has significant carboxyhemoglobin levels, which remain unaltered even after 3 weeks storage (32). Because the blood that contains carboxyhemoglobin interferes with oxygen release, smokers should be advised to stop smoking for at least 12 hr before they donate blood.

In summary, our data show that smoking increases carboxyhemoglobin concentration in the blood that results in a decrease in available hemoglobin for oxygen transport. Carboxyhemoglobin also shifted P_{50} to the left. After smoking is stopped for 12 hr, there is a significant decrease in carboxyhemoglobin levels and an increase in P_{50} of the oxyhemoglobin. We conclude that preoperative smoking halt for as little as 12 hr is enough to shift P_{50} towards near normal in patients who smoke one to two packs of cigarettes per day.

References

1. Castledan CM, Cole PV. Variations in carboxyhemoglobin levels in smokers. *Br Med J* 1974;4:736-8.
2. Roughton FJW, Darling RC. The effect of carbon monoxide on the oxyhemoglobin dissociation curve. *Am J Physiol* 1944;141:17.
3. Ayres SM, Giannelli S, Jr, Mueller H. Myocardial and systemic responses to carboxyhemoglobin. *Ann NY Acad Sci* 1970;174:268-93.
4. Anderson EW, Andelman RJ, Strauch JM, Fortuin NJ, Knelson JH. Effect of low level carbon monoxide exposure on onset and duration of angina pectoris. *Ann Intern Med* 1973;79:46-50.
5. Stonesifer LD. How carbon monoxide reduces plasma volume. *N Engl J Med* 1978;299:311-12.
6. Ramsdale DR, et al. Smoking and coronary artery disease assessed by routine coronary arteriography. *Br Med J* 1985;290:197-200.
7. Morton HJV. Tobacco smoking and pulmonary complications after operation. *Lancet* 1944;i:368-70.
8. Wightman JAK. A prospective survey of the incidence of postoperative pulmonary complications. *Br J Surg* 1968;55:85-91.
9. Laszlo G, Archer GA, Darrell JH, Dawson JM, Fletcher CM. The diagnosis and prophylaxis of pulmonary complications of surgical operation. *Br J Surg* 1973;60:129-34.
10. Chalon J, Tayyab MA, Ramanathan S. Cytology of respiratory epithelium as a predictor of respiratory complications after operation. *Chest* 1975;67:32-5.
11. Sonnefeldt T, Wennmalm A. Inhibition by nicotine of the formation of prostacyclin-like activity in rabbit and human vascular tissue. *Br J Pharmacol* 1980;71:609-15.
12. Stoel I, Gressen WJ, Zwolsman E. Direct effect of nicotine on prostacyclin production in human umbilical arteries. *Acta Ther* 1980;6(Suppl 4):32-7.
13. Moncada S, Vane JR. Arachidonic acid metabolites and interactions between platelets and blood vessel walls. *N Engl J Med* 1979;300:1142-5.
14. Wennmalm A. Interaction of nicotine and prostaglandins in the cardiovascular system. *Prostaglandins* 1982;23:139-45.
15. McGill HC Jr. Potential mechanisms for the augmentation of atherosclerosis on arterio sclerotic disease by cigarette smoking. *Prev Med* 1979;8:390-9.
16. Ball K, Turner R. Smoking and the heart. *Lancet* 1974;ii:822-6.
17. Greenspan K, Edmonds RE, Knoebel SB, Fisch C. Some effects of nicotine on cardiac automaticity, conduction and ionotropy. *Arch Intern Med* 1969;123:707-12.
18. Turino GM. Effect of carbon monoxide on the cardiorespiratory system. *Circulation* 1981;63:253A-259A.
19. Kaul B, Calabro J, Hutcheon DE. Effects on carbon monoxide on the vulnerability of the ventricles to drug induced arrhythmias. *J Clin Pharm* 1974;14:25-31.
20. Aronow WS, Cassidy J, Vangrow JS, et al. Effects of cigarette smoking and breathing carbon monoxide on cardiovascular hemodynamics in anginal patients. *Circulation* 1974;50:340-7.
21. Roth GM, Shick RM. The cardiovascular effects of smoking with special reference to hypertension. *Ann NY Acad Sci* 1960;90:308-16.
22. Comroe JH Jr. The pharmacological actions of nicotine. *Ann NY Acad Sci* 1960;90:48-51.
23. Gebber GL. Neurogenic basis for the rise in blood pressure evoked by nicotine in the cat. *J Pharmacol Exp Ther* 1969;166:255-63.
24. Cryer PE, Haymond MW, Santiago JV, Shah SD. Norepinephrine and epinephrine release and adrenergic mediation of smoking associated hemodynamic and metabolic events. *N Engl J Med* 1976;295:573-7.
25. Mitchell C, Garrahy P, Peake P. Postoperative respiratory morbidity: identification and risk factors. *Aust NZ J Surg* 1982;52:203-9.
26. Hill D, Larcombe I, Reffhange JG. Smoking and impairment of performance. *Med J Aust* 1978;2:60-3.
27. Rode A, Shephard RJ. The influence of cigarette smoking upon the oxygen cost of breathing in near maximal exercise. *Med Sci Sports Exerc* 1971;3:51-3.
28. Seppanen A. Physical work capacity in relation to carbon monoxide inhalation and tobacco smoking. *Ann Clin Res* 1977;9:269-74.
29. Smith JR, Landaw SA. Smokers' polycythemia. *N Engl J Med* 1978;298:6-10.
30. Forster RE. Carbon monoxide and the partial pressure of oxygen in tissue. *Ann NY Acad Sci* 1970;174:233-41.
31. Nunn JF. Applied respiratory physiology, second edition. London-Boston:Butterworths, 416-9, 1978.
32. Millar RA, Gregory IC. Reduced O_2 content in equilibrated fresh heparinized and ACD-stored blood from cigarette smokers. *Br J Anaesth* 1972;44:1015-9.

Comparison of Propofol with Methohexital for Outpatient Anesthesia

Van A. Doze, BS, Lynn M. Westphal, BA, and Paul F. White, PhD, MD

DOZE VA, WESTPHAL LM, WHITE PF. Comparison of propofol with methohexital for outpatient anesthesia. *Anesth Analg* 1986;65:1189-95.

Propofol is an intravenous anesthetic currently available for clinical investigative use. The intraoperative and postoperative effects of propofol were compared to methohexital when used as an adjuvant to nitrous oxide for outpatient anesthesia. Sixty healthy young women were randomly assigned to receive either methohexital, 1.5 mg/kg intravenously (IV), or propofol, 2.5 mg/kg IV, for induction of anesthesia. Both drugs produced transient cardiovascular and respiratory depression after induction. Maintenance of anesthesia consisted of either methohexital, 6 ± 2 mg/min,

or propofol, 7 ± 2 mg/min (mean \pm SD) by continuous infusion in combination with nitrous oxide, 70% in oxygen. Use of a propofol infusion was associated with lower blood pressures and heart rates during maintenance. Propofol was associated with fewer side effects (e.g., hiccoughing, nausea, and vomiting) intra- and postoperatively. Recovery times for awakening, orientation, and ambulation were consistently shorter with propofol. We conclude that propofol is a useful alternative to methohexital for induction and maintenance of outpatient anesthesia.

Key Words: ANESTHETICS, INTRAVENOUS—methohexital; propofol. ANESTHESIA—outpatient.

The increasing popularity of outpatient surgery has prompted the search for new anesthetic agents that can provide safe and effective anesthesia with a rapid recovery. Propofol (Diprivan®), a 2,6-sterically hindered substituted phenol, is a rapid and short-acting intravenous (IV) anesthetic. Because it is virtually insoluble in aqueous solution, propofol was initially solubilized in a Cremophor solution. Although early studies in Europe demonstrated that the drug was an effective anesthetic induction agent, the solvent (Cremophor) was associated with a high incidence of untoward hypersensitivity reactions (1). Recently, propofol was reformulated in an aqueous emulsion containing 10% soya bean oil, 1.2% egg phosphatide and 2.25% glycerol (2). The reformulated drug has been administered to over 1500 patients worldwide, with no definite evidence of specific toxicity attributable to propofol (Stark RD, personal communication).

Methohexital (Brevital®) is a popular drug for induction and maintenance of anesthesia in outpatients

because its use appears to be associated with a more rapid recovery than other widely used IV anesthetics, e.g., thiopental (Pentothal®) and etomidate (Amidate®) (3,4). However, the use of methohexital is associated with excitatory side effects during induction (e.g., myoclonus, hiccoughing) and on occasion, excessive drowsiness ("hangover") has been noted during the early postoperative period.

We designed a study to assess the safety, efficacy, and recovery characteristics of the new emulsion formulation of propofol when compared with methohexital for induction and maintenance of general anesthesia during brief outpatient procedures.

Methods

Sixty healthy (ASA physical status I or II), young women presenting for brief outpatient gynecologic procedures (<45 min duration) were randomly assigned to either a propofol or methohexital treatment group. The study was approved by the Institutional Committee on Human Research, and written informed consent was obtained from each patient. The two groups were comparable with respect to age, weight, ASA physical status, race, smoking history, and type of operative procedure. Patients with a history of allergic reactions to any of the study drugs were excluded.

This study was supported in part by funds from the Anesthesia-Pharmacology Research Foundation.

Received from the Department of Anesthesia, Stanford University School of Medicine, Stanford, California. Accepted for publication April 28, 1986.

Address correspondence to Dr. White, Department of Anesthesia, S-268C, Stanford University Medical Center, Stanford, CA 94305.

Table 1. Demographic and Preoperative Vital Signs in the Two Drug Treatment Groups

Item	Methohexital		Propofol	
	Mean \pm SD	Range	Mean \pm SD	Range
Age (yr)	26.7 \pm 7.4	16-44	25.9 \pm 6.7	16-39
Weight (kg)	62.1 \pm 13.9	43.2-100	60.8 \pm 11.7	41.8-96.4
Oral temp ($^{\circ}$ C)	36.9 \pm 0.3	36.2-37.5	36.9 \pm 0.3	35.8-37.4
Systolic BP (mm Hg)	108.1 \pm 11.6	80-140	109.5 \pm 10.3	90-130
Diastolic BP (mm Hg)	66.9 \pm 8.3	50-84	64.8 \pm 10.8	40-90
Heart rate (beats/min)	79.3 \pm 9.9	60-100	79.9 \pm 9.4	64-100
Respirations (breaths/min)	17.6 \pm 2.4	16-24	17.4 \pm 2.2	11-20

SD, standard deviation.

Prior to surgery, these unpremedicated patients were asked to complete a questionnaire. Upon arrival in the operating room, an 18-gauge IV catheter was inserted into a forearm or antecubital vein. Routine monitoring devices included a precordial stethoscope, an ECG, and a DinamapTM blood pressure cuff. Mean arterial pressure (MAP) and heart rate (HR) were recorded at 1-3-min intervals. The end-tidal carbon dioxide (PETCO₂) and respiratory rate (RR) were continuously monitored using a Puritan BennettTM capnograph. The CO₂ sampling catheter was connected at the elbow junction on the face mask. The Datex Anesthesia and Brain Activity MonitorTM was used to continuously record electromyographic (EMG) activity with cutaneous gel electrodes placed on the forehead and mastoid regions.

In order to decrease the anesthetic requirement (5), all patients received meperidine (Demerol®), 1 mg/kg IV, 3-5 min prior to induction of anesthesia. In the propofol group ($n = 30$), anesthesia was induced with propofol, 2.5 mg/kg IV, over 15-60 sec, and maintained with a propofol infusion, 2.5 mg/ml IV, in combination with nitrous oxide (N₂O), 70% in oxygen. The methohexital group ($n = 30$) received methohexital, 1.5 mg/kg IV, over 15-60 sec, and a maintenance infusion of methohexital, 1.5 mg/ml IV, in combination with N₂O, 70% in oxygen. If the patient did not fall asleep within 1 min after the initial induction dose, supplemental doses of the study drugs (e.g., propofol, 10-15 mg, or methohexital, 5-10 mg) were administered until loss of consciousness was achieved. The time from the start of the bolus injection to the abolition of the eyelash reflex was recorded as the induction time. When the patient became unresponsive, N₂O, 70% in oxygen, was administered via a tightfitting face mask using a conventional circle absorber system. The maintenance infusion was initiated within 3 min from the start of induction in all patients. The initial maintenance infusion rates for propofol and methohexital were 4-6 mg/min and 3-5 mg/min, respectively.

An attempt was made to maintain a stable level of anesthesia (e.g., constant respiratory rate, absence of movement) by varying the rate of the maintenance infusion in response to clinical signs. The infusion rate was increased when the patient showed clinical signs of inadequate anesthesia (e.g., increases in muscle tone, respiratory rate, blood pressure, or heart rate) in response to surgical stimulation. The maintenance infusion rate was decreased if the patient showed evidence of excessive drug effect (e.g., progressive slowing of respiratory rate or decreases in muscle tone). At the end of the operation, the anesthetic infusion and N₂O were discontinued.

Recovery times were recorded as follows: awakening time (elapsed time from discontinuation of nitrous oxide until the patient spontaneously opened eyes); response time (time until the patient responded to a simple verbal command); orientation time (time until the patient was oriented to person and place); and ambulation time (time until the patient could walk unassisted). In calculating the average ambulatory time for each group, patients with protracted nausea and vomiting were excluded. Postoperatively, patients were asked to repeat the questionnaire rating the subjective quality of the anesthetic. All side effects were recorded, and appropriate therapy administered (e.g., antiemetics for nausea and vomiting, acetoaminophen with codeine for lower abdominal pain or headache).

Data are reported as mean values \pm standard deviation (SD). Data from the two groups were compared using Statistical Analysis System one-way analysis of variance with Wilcoxon rank sum test (for continuous variables) and χ^2 -test (for categorical variables), with a P value < 0.05 considered statistically significant.

Results

The two study groups were comparable with respect to demographic data and baseline cardiorespiratory values (Table 1). The onset of anesthesia was rapid

Table 2. Methohexital and Propofol Dosage Requirements For Induction and Maintenance of Anesthesia

	Methohexital		Propofol	
	Mean \pm SD	Range	Mean \pm SD	Range
Induction				
Dose (mg/kg)	1.5 \pm 0.1	1.2-1.7	2.5 \pm 0.2	2.0-2.7
Total dose (mg)	92 \pm 18	60-145	149 \pm 23	105-192
Onset time (sec)	50 \pm 36	15-165	44 \pm 14	30-60
Maintenance				
Infusion rate (mg/min)	6 \pm 2	3-11	7 \pm 2	4-12
Infusion dose (mg)	113 \pm 50	57-300	109 \pm 42	45-235
Infusion time (min)	19 \pm 7	9-45	16 \pm 6	6-33
Anesthesia time (min) ^a	23 \pm 8	13-57	21 \pm 5	11-37

^aTime from injection of induction dose until N₂O is discontinued.
SD, standard deviation.

(<60 sec), with total induction doses of methohexital and propofol equal to 92 \pm 18 mg and 149 \pm 23 mg, respectively (Table 2). Transient apnea (lasting 60-75 sec) occurred in approximately one third of the patients with both methohexital and propofol. Other common side effects during induction were pain on injection and hiccoughing (Table 3). The maintenance infusion time and duration of anesthesia did not differ significantly between the two treatment groups (Table 2).

During the maintenance period, the average infusion rates were similar for both drugs. The earliest clinical signs of inadequate anesthesia were tachypnea, increased muscle tone, and gross motor activity.

Table 3. Side Effects during the Perioperative Period in the Two Drug Treatment Groups

Period	Methohexital(%)	Propofol(%)
Induction		
Transient apnea	30	30
Pain on injection	7	17
Hiccoughing	17	7
Respiratory problems ^a	17	13
Myoclonus	3	0
Headache	0	3
Maintenance		
Flushing	3	0
Hiccoughing	3	0
Respiratory problems ^a	13	0
Recovery		
Headache	7	13
Dizziness	13	7
Nausea/vomiting	43	17 ^b
Hiccoughing	3	0
Itching	0	3

^aIncluding bronchospasm, laryngospasm, or coughing.

^bSignificantly different from methohexital group, $P < 0.05$.

In general, patients showed these signs before any changes were noted in heart rate or mean arterial pressure. Both methohexital and propofol appeared to be associated with acceptable cardiorespiratory stability, but significant differences were noted between the two groups (Fig. 1). Whereas hemodynamic val-

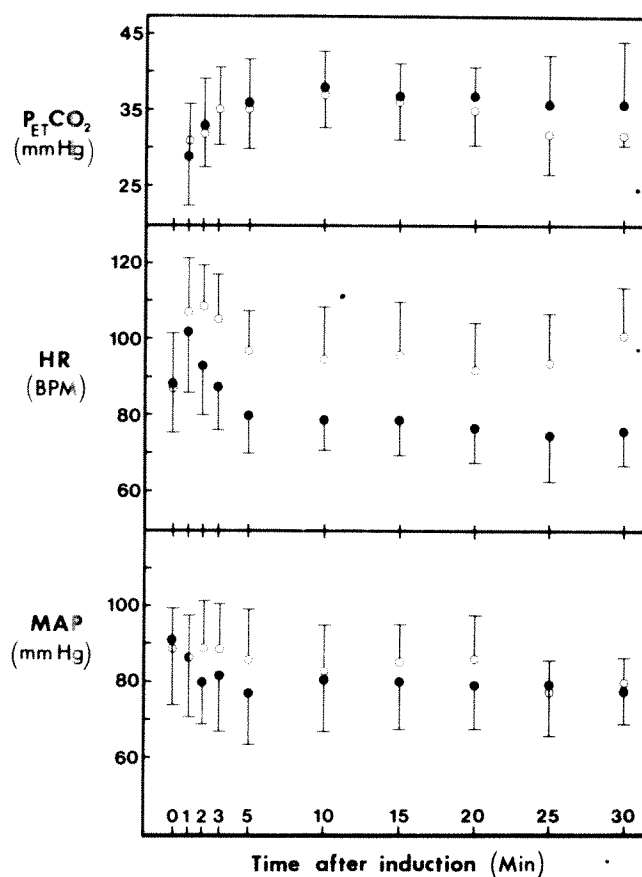


Figure 1. Comparative effects of methohexital (○) and propofol (●) on mean arterial pressure (MAP), heart rate (HR), and end-tidal CO₂ (PETCO₂).

Table 4. Effect of Methohexital and Propofol on the Amplitude of Electromyographic (EMG) Activity

	EMG amplitude				<i>P</i> value
	Methohexital		Propofol		
	Mean \pm SD	Range	Mean \pm SD	Range	
Awake	68 \pm 8	50-82	69 \pm 7	53-85	0.62
3 Min after induction	19 \pm 7	10-34	9 \pm 4	6-22	0.01
Maximal surgical stimulation	58 \pm 16	23-85	36 \pm 18	10-87	0.01
End of anesthesia (N ₂ O off)	69 \pm 12	47-86	68 \pm 10	52-85	0.95

SD, standard deviation.

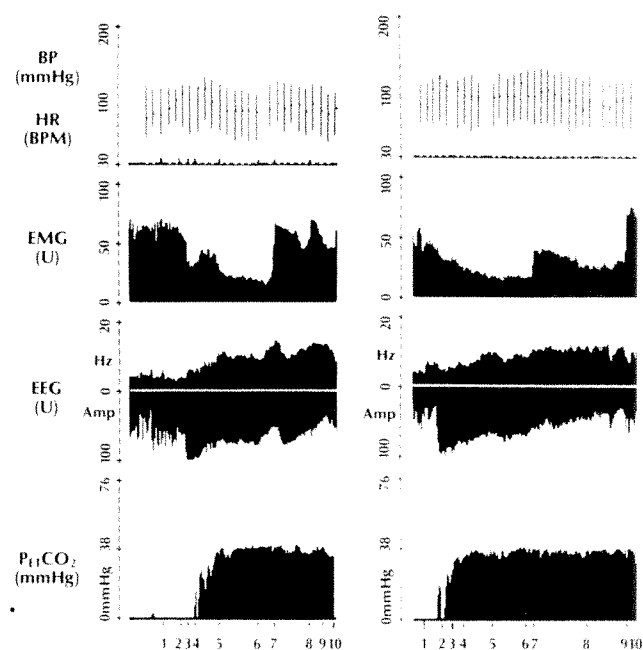


Figure 2. Characteristic examples of changes in hemodynamic variables, EMG activity and P_{ETCO_2} in patients receiving methohexital for induction and maintenance of anesthesia. The numbers on the abscissa correspond to the following events: 1, meperidine 1 mg/kg IV; 2, methohexital 1.5 mg/kg IV bolus; 3, nitrous oxide 70%; 4, methohexital infusion (3 mg/min); 5, surgical preparation; 6, start surgery; 7, maximal surgical stimulation; 8, end infusion; 9, discontinued N₂O; and 10, patient awake.

ues at 1 min did not differ between the two groups, statistically significant differences in systolic blood pressure and heart rate were seen 2, 3, 5, 10, 15, and 20 min after induction. Propofol was associated with decreases in systolic, diastolic, and mean arterial pressure, whereas blood pressure was unchanged in the methohexital group. Heart rates were significantly higher in patients receiving methohexital. Changes in respiratory rate and end-tidal CO₂ values did not differ significantly between drug treatments. Side effects during the maintenance period were similar in both treatment groups (Table 3).

Propofol and methohexital had different effects on the EMG during the induction and maintenance (Ta-

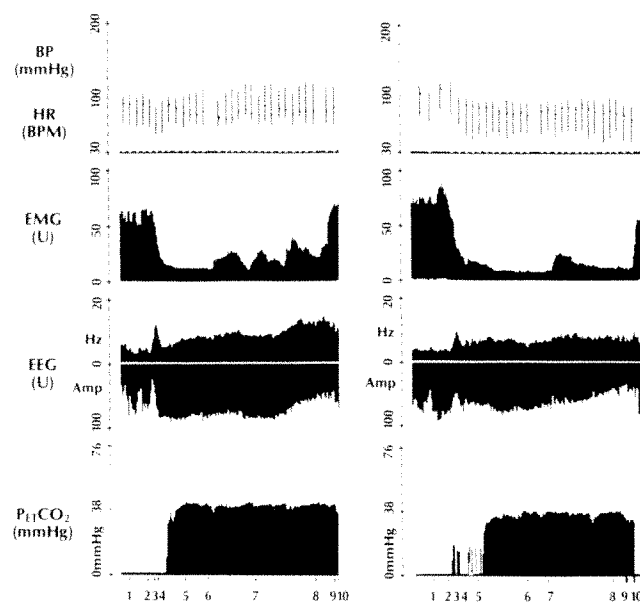


Figure 3. Characteristic examples of changes in hemodynamic variables, EMG activity, and P_{ETCO_2} in patients receiving propofol for induction and maintenance of anesthesia. The numbers on the abscissa correspond to the following events: 1, meperidine 1 mg/kg IV; 2, propofol 2.5 mg/kg IV bolus; 3, nitrous oxide 70%; 4, propofol infusion (4 mg/min); 5, surgical preparation; 6, start surgery; 7, maximal surgical stimulation; 8, end infusion; 9, discontinued N₂O; and 10, patient awake.

ble 4, Figs. 2, 3). The induction dose of propofol produced a significantly greater decrease in EMG activity (87% less than the baseline EMG value) than methohexital (72% less than the baseline EMG value). In addition, a greater increase in the EMG activity was recorded during maximal surgical stimulation with methohexital than with propofol (85 and 52% of baseline EMG values, respectively).

Although the awakening and response times were similar in both groups, the times to orientation and ambulation were 2.5 ± 1.4 and 67 ± 24 min, respectively, with propofol compared to 3.6 ± 1.9 and 81 ± 23 min after methohexital (Table 5). The difference between the two groups with respect to the ambula-

Table 5. Postoperative Recovery Times in the Two Treatment Groups

Recovery times	Methohexital (mean \pm SD)	Propofol (mean \pm SD)	P value
Time from end of maintenance infusion to:			
Awakening (min)	5.6 \pm 3.1	5.0 \pm 2.2	0.69
Response (min)	6.0 \pm 3.2	5.4 \pm 2.2	0.61
Orientation (min)	6.4 \pm 3.2	5.6 \pm 2.3	0.61
Time from nitrous oxide off to:			
Awakening (min)	2.9 \pm 1.8	1.9 \pm 1.3	0.06
Response (min)	3.3 \pm 1.9	2.3 \pm 1.3	0.09
Orientation (min)	3.6 \pm 1.9	2.5 \pm 1.4	0.02
Ambulation (min)	81 \pm 23	67 \pm 24	0.04

SD, standard deviation.

tion time was minimized because a larger number of patients receiving methohexital (seven vs one) were excluded as a result of protracted nausea and vomiting.

Postoperatively, nausea and vomiting occurred more frequently with methohexital (43%) than with propofol (17%). Results of the recovery questionnaire also indicated that a significantly larger number of patients reported nausea and tremulousness with methohexital (57 and 28%, respectively) than with propofol (14 and 7%, respectively). Incidences of other postoperative side effects with methohexital and propofol are summarized in Table 3.

Discussion

Outpatient surgery requires anesthetic drugs and techniques that provide safe and effective anesthesia with a rapid recovery and minimal anesthetic-related side effects (6). With the rising concern over anesthetic gas pollution, attention has focused on the development of intravenous anesthetics with a rapid onset and short duration of action. Currently, methohexital is considered by many to be the intravenous anesthetic of choice when a rapid recovery is required. Unfortunately, its use may be associated with undesirable side effects both during and after surgery.

Propofol, a rapid and short-acting intravenous anesthetic, was recently introduced in this country for clinical investigation. In our study, we found that propofol provided a rapid, smooth, and pleasant loss of consciousness. In contrast to methohexital, hiccoughing was not a problem with propofol. Consistent with other recently published studies (7-10), the most common side effects noted during induction with propofol were transient apnea (30%) and pain on injection (17%). Postoperatively, only two patients in the propofol group recalled discomfort during induction of anesthesia. The incidence of pain on injection with propofol appears to be related to the size of the

vein into which the drug is injected. When small hand veins are used, a significantly higher incidence of pain is reported during induction (11). The use of narcotic premedication can decrease both the incidence of pain on injection and the induction time (e.g., loss of eyelash reflex) (12); however, it may also increase the incidence and duration of apnea after a large bolus dose of propofol used for induction (13).

When used for the induction of anesthesia in outpatients, propofol has been reported to produce significantly more cardiovascular and respiratory depression than thiopental, methohexital, or etomidate (7-10). In agreement with these studies, we also noted more profound cardiovascular depression with propofol (Fig. 1). However, we found no statistically significant difference between methohexital and propofol with respect to the incidence and duration of apnea during induction. Although previous investigators found no relationship between the speed of injection and the degree of respiratory depression produced by propofol (14), we noted a lower incidence of apnea when the induction dose was administered over 45-60 sec (compared to 15-30 sec).

Methohexital and propofol were both associated with cardiorespiratory stability during maintenance. Whereas methohexital was not associated with a significant change in arterial pressure, it did produce a persistent increase in heart rate (Fig. 2). Propofol, on the other hand, decreased both arterial blood pressure and heart rate. The depressant effects on the cardiovascular system occurred within 5 min after induction and subsequently remained stable during maintenance. As a result of its cardiovascular depressant properties, propofol should be used with caution in patients with limited cardiovascular reserve as well as in those with cerebrovascular disease.

Although larger doses of propofol (vs methohexital) were administered for induction of anesthesia, maintenance infusion rates subsequently required to

suppress clinical responses to surgical stimulation were similar. These data indicate that the potency difference between propofol and methohexital may be less than we initially assumed on the basis of previous induction studies (15,16). Our average maintenance infusion rates for methohexital (97 $\mu\text{g/kg/min}$) and propofol (115 $\mu\text{g/kg/min}$) are consistent with earlier studies in the anesthesia literature in which infusions of methohexital or propofol (Cremophor) were administered as adjuvants to nitrous oxide (3,17,18).

The incidence of purposeful movements in response to surgical stimulation did not differ significantly in our two treatment groups. However, propofol appeared to be more effective than methohexital in suppressing the EMG activity during the operation. Given the more prominent depressant effects of propofol on EMG activity, these data are consistent with studies that indicate that propofol might potentiate the analgesic and neuromuscular relaxant properties of opioid analgesics and nondepolarizing muscle relaxants (19,20). Alternatively, these data (e.g., lower EMG activity, heart rate, blood pressure) might indicate that a greater "depth of anesthesia" was achieved with the propofol infusion. Nevertheless, recovery times were consistently shorter with propofol than with methohexital. Furthermore, Mackenzie and Grant (7) found less postoperative impairment of cortical reaction time and critical flicker fusion threshold when propofol was used for induction of anesthesia (compared with methohexital and thiopental).

Ideally, this study would have been performed in a double-blinded fashion. However, this was not feasible because of the marked differences in appearance of these two anesthetics. Methohexital is a clear solution, whereas propofol has a characteristic "milky" white appearance. An attempt was made to maintain a comparable depth of anesthesia during the operation with both drugs (i.e., absence of purposeful movement, stable cardiorespiratory parameters) in this homogenous population of healthy young outpatients. Furthermore, the recovery times and postoperative side effects were recorded by a blinded observer.

The rapid recovery and low incidence of side effects when propofol was used for induction and maintenance of anesthesia may result in an earlier discharge after outpatient surgery. In addition, the low incidence of side effects associated with propofol during maintenance suggests that propofol may be an acceptable alternative to the volatile anesthetics and/or nitrous oxide. Carefully controlled studies comparing a propofol infusion (as an adjuvant to N_2O) with standard inhalational anesthetic techniques are clearly needed. Finally, although no hypersensitivity reactions were observed in this study, the true incidence

of reactions to the propofol emulsion will only be determined in large-scale clinical trials.

In summary, propofol is a smooth, rapid-acting sedative-hypnotic compound with significant cardiorespiratory depressant properties that would appear to be a useful alternative to the currently available intravenous agents in situations (e.g., outpatient surgery) where early ambulation and discharge is advantageous.

The authors wish to thank Dr. William A. Dworsky for his support and cooperation during this investigation. Special thanks to Steven E. Strand and Dr. Gustavo Acosta for their assistance with the statistical analyses, and to Roz Mandell for her assistance in preparing the manuscript. Stuart Pharmaceuticals, Division of ICI Americas Inc., is also acknowledged for their support of the study.

References

1. Clarke RSJ, Dundee JW, Garrett RT, McArdle GK, Sutton JA. Adverse reactions to intravenous anaesthetics: a survey of 100 reports. *Br J Anaesth* 1975;47:575-85.
2. Glen JB, Hunter SC. Pharmacology of an emulsion formulation of ICI 35868. *Br J Anaesth* 1984;56:617-26.
3. White PF. Continuous infusions of thiopental, methohexital or etomidate as adjuvants to nitrous oxide for outpatient anesthesia (abstr). *Anesth Analg* 1984;63:282.
4. Whitwam JG. Methohexitone (editorial). *Br J Anaesth* 1976;48:617-9.
5. White PF, Chang T. Effect of narcotic premedication on the intravenous anesthetic requirement. *Anesthesiology* 1984;61:A389.
6. White PF. Anesthesia for ambulatory surgery. In: Stoelting, Barash, Gallagher, eds. *Advances in Anesthesia*. Chicago: Year Book Medical Publishers, Inc., 1985:1-29.
7. MacKenzie N, Grant IS. Comparison of the new emulsion formulation of propofol with methohexitone and thiopentone for induction of anaesthesia in day cases. *Br J Anaesth* 1985;57:725-31.
8. Wells JKG. Comparison of ICI 35868, etomidate and methohexitone for day-case anaesthesia. *Br J Anaesth* 1985;57:732-5.
9. Mouton SM, Bullington J, Davis L, Fisher K, Ramsey S, Wood M. A comparison of Diprivan and thiopental for the induction of anesthesia. *Anesthesiology* 1985;63:A364.
10. Grounds RM, Twigley AJ, Carli F, Whitwam JG, Morgan M. The haemodynamic effects of intravenous induction: comparison of the effects of thiopentone and propofol. *Anaesthesia* 1985;40:735-40.
11. Hynynen M, Korttila K, Tammisto T. Pain on IV injection of propofol (ICI 35868) in emulsion formulation. *Acta Anaesthesiol Scand* 1985;29:651-2.
12. Fragen RJ, de Grood PM, Robertson EN, Booij LHDJ, Crul JF. Effects of premedication on Diprivan induction. *Br J Anaesth* 1982;54:913-6.
13. Briggs LP, Bahar M, Beers HTB, et al. Effect of preanaesthetic medication on anaesthesia with ICI 35 868. *Br J Anaesth* 1982;54:303-6.

14. Rolly G, Versichelen L, Huyghe L, Mungroop H. Effect of speed of injection on induction of anaesthesia using propofol. *Br J Anaesth* 1985;57:743-6.
15. Major E, Verniquet AJW, Waddell TK, Savege TM, Hoffler DE, Aveling W. A study of three doses of ICI 35868 for induction and maintenance of anaesthesia. *Br J Anaesth* 1981;53:267-72.
16. Cummins GC, Dixon J, Kay NH, et al. Dose requirements of ICI 35,868 (Propofol, 'Diprivan') in a new formulation for induction of anaesthesia. *Anaesthesia* 1984;39:1168-71.
17. Prys-Roberts C, Sear JW, Low JM, Phillips KC, Dagnino J. Hemodynamic and hepatic effects of methohexital infusion during nitrous oxide anesthesia in humans. *Anesth Analg* 1983;62:317-23.
18. Prys-Roberts C, Davies JR, Calverley RK, Goodman NW. Haemodynamic effects of infusions of diisopropyl phenol (ICI 35868) during nitrous oxide anaesthesia in man. *Br J Anaesth* 1983;55:105-11.
19. Briggs LP, Dundee JW, Bahar M, Clarke RSJ. Comparison of the effect of diisopropyl phenol (ICI 35868) and thiopentone on response to somatic pain. *Br J Anaesth* 1982;54:307-11.
20. Robertson EN, Fragen RJ, Booij LHDJ, Van Egmond J, Crul JF. Some effects of diisopropyl phenol (ICI 35 868) on the pharmacodynamics of atracurium and vecuronium in anaesthetized man. *Br J Anaesth* 1983;55:723-8.

Cerebral Arteriovenous Oxygen Content Difference during Barbiturate Therapy in Patients with Acute Brain Damage

Atsuo Sari, MD, Yasutoshi Matayoshi, MD, Akitomo Yonei, MD, Hiroko Ogasahara, MD, Tadahiko Nonoue, MD, Kimio Yokota, MD, and Shigeki Yamashita, MD

SARI A, MATAYOSHI Y, YONEI A, OGASAHARA H, NONOUE T, YOKOTA K, YAMASHITA S. Cerebral arteriovenous oxygen content difference during barbiturate therapy in patients with acute brain damage. *Anesth Analg* 1986;65:1196-1200.

This study evaluated the reliability of cerebral blood flow equivalent (CBFE), which was calculated as the reciprocal of cerebral arteriovenous oxygen content difference ($C(av)DO_2$) as a monitor during barbiturate therapy in patients with cerebral ischemic insults. A barbiturate (thiamylal) was administered at a rate of $3 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{hr}^{-1}$ for 2-5 days to four patients who had suffered cardiac arrest, four with acute

focal ischemia, two with postoperative brain edema after neurosurgery, and one with brain damage due to asphyxia. Four of the 11 patients completely recovered neurologically (recovery group), and others had neurological sequelae or died (nonrecovery group). The mean value of CBFE in the recovery group decreased significantly with barbiturate therapy to $13 \pm 1 \text{ ml blood/ml O}_2$ from $39 \pm 3 \text{ ml blood/ml O}_2$ but did not decrease in the nonrecovery group. We conclude that CBFE can be useful for monitoring the effect of barbiturate therapy in ischemic brain insults.

Key Words: BRAIN, COMA—barbiturate therapy. HYPNOTICS, BARBITURATES—brain injury.

Although respiratory, ocular and motor signs help in judging whether patients are improving or worsening during the period immediately after acute brain ischemia, it is impossible to follow a patient's neurological state when a muscle relaxant or barbiturate is used to control either ventilation or increased intracranial pressure (ICP). ICP measurement has been used as a monitor during barbiturate therapy (1,2) but it is not always available in all institutes. In this study we examined the usefulness of the cerebral blood flow equivalent (CBFE) and/or the cerebral arteriovenous oxygen content difference ($C(av)DO_2$) as the bedside monitor in the management of patients with barbiturate therapy for acute brain insults.

Methods

We studied 11 patients (average age 57 yr) admitted directly or referred to the ICU of our hospital 4-8 hr after cerebral ischemic insults. They were not responsive to pain and were not spontaneously talking.

Table 1 summarizes the clinical features of these patients.

All patients were ventilated mechanically (Servo 900-B or Bennett MA-1) to maintain normocarbida and PaO_2 within 80-120 mm Hg. According to the Glasgow Coma Scale (3), the state of consciousness of the 11 patients on admission was 3-4. In all patients the electroencephalogram (EEG) was recorded by frontoparietal silver-silver chloride electrodes. Catheters were placed percutaneously into the radial artery or dorsal pedis artery for pressure measurement and blood sampling and an intravenous catheter (Argyle Medi-Cut catheter #18) was introduced percutaneously into the internal jugular vein (IJV) and passed distally to the inferior jugular bulb for sampling of cerebral venous blood. The method of IJV puncture used was that described by Yonei et al. (4), with ultrasonic real-time guidance. The position of the catheter's tip was confirmed radiographically. In the patients who had a unilateral cerebral lesion, the catheter was placed into the contralateral IJV. A Swan-Ganz catheter or central venous catheter (Argyle Medi-Cut catheter #16) was placed percutaneously into the pulmonary artery or central vein for monitoring systemic hemodynamics. When systemic hemodynamics had become stable, arterial and internal jugular venous blood was sampled anaerobically before administration of the

Received from the Department of Anesthesia, Kurashiki Central Hospital, Okayama, Japan. Accepted for publication June 30, 1986.

Address correspondence to Dr. Sari, Department of Anesthesia, Kurashiki Central Hospital, 1-1-1 Miwa, Kurashiki, Okayama 710, Japan.

Table 1. Clinical Data

Patient number	Age (yr)	Sex	Diagnosis	Glasgow Coma Scale	Barbiturate			Outcome
					Timing (hr)	Duration (hr)	Dose (g)	
1	41	M	Cardiac arrest; thoracic trauma	3	8	48	9.60	Vegetative
2	68	F	Cardiac arrest; left cerebral infarction	3	9	48	8.40	Death
3	60	M	Cardiac arrest; myocardial infarction	3	8	48	8.16	Death
4	16	F	Cardiac arrest; mitral valve prolapse	4	7	13	1.40	Severe disability
5	61	M	Strangulation	4	4	48	9.60	Good recovery
6	61	F	Right intracerebral hemorrhage	4	28	48	6.30	Good recovery
7	70	M	Left cerebral infarction	4	13	48	9.60	Good recovery
8	64	F	Postoperative brain edema (craniopharyngioma)	3	24	48	6.30	Death
9	72	M	Head injury	4	5	132	53.04	Good recovery
10	68	F	Head injury	4	48	120	8.50	Vegetative
11	50	M	Postoperative brain edema (MCA clipping)	4	24	58	11.64	Death

Abbreviations: M, male; F, female; MCA, middle cerebral artery; Timing (hr), time from cerebral insults to the start of barbiturate therapy; Duration (hr), period of barbiturate therapy; Dose (g), total dose of thiamylal.

barbiturate. Arterial and cerebral venous PO_2 , PCO_2 , and pH were measured with an IL meter (Instrumentation Laboratory, MA). The arterial and cerebral venous oxygen content (CaO_2 , CvO_2) was measured in duplicate with Lex O_2 Con (Lexington Instrument, MA), which had been validated for clinical study (5). The blood samples were placed in an ice bath prior to measurement, and calibration of these instruments was done by the same person throughout the study period. Cerebral blood flow equivalent (6) was calculated as the reciprocal of $C(av)DO_2$ as follows:

$$CBFE = CBF/CMRO_2$$

where CBF is cerebral blood flow and $CMRO_2$ is cerebral metabolic rate for oxygen. The normal value for CBFE is 14–15 ml blood/ml O_2 . During these measurements, expired CO_2 concentration was monitored (Medical gas analyzer LB-2, Beckmann, IL), and $PaCO_2$ was maintained constant for at least 20 min by controlled mechanical ventilation.

Thiamylal was administered at an initial rate of 3 $mg \cdot kg^{-1} \cdot hr^{-1}$, followed by 4 mg/kg bolus intravenous (IV) injections with the frequency titrated according to changes in the EEG. In patients with some EEG activity before the barbiturate was given, the thiamylal was given until the EEG showed "burst and suppression." In patients with isoelectric EEGs, the infusion rate of barbiturate was fixed at 3 $mg \cdot kg^{-1} \cdot hr^{-1}$. The EEG was monitored continuously before, during, and after barbiturate therapy. Dopamine was infused

intravenously to prevent hypotension during barbiturate therapy in some patients. Mannitol and steroids were also given in combination with barbiturate therapy: mannitol 1 mg/kg IV for 30 min every 6 hr for 48 hr, and dexamethazone as an initial IV dose of 1 mg/kg followed by 0.2 mg/kg every 6 hr for 24 hr. Measurements during barbiturate therapy were made 4–6 hr after the administration of barbiturate. Barbiturate therapy was continued for 48–132 hr as needed. Measurements were repeated 2–3 days after discontinuation of barbiturate administration. Patients' outcomes were evaluated at discharge from ICU by the Glasgow outcome scale described by Jennet and Bond (7) with the 11 patients divided into the two groups: recovery and nonrecovery. The former group included patients who had complete neurological recovery; the latter, patients who recovered with neurological sequelae or died. Body temperature and hemoglobin concentration were maintained in the range of 36–38°C and 10–12 g/dl, respectively.

All values are expressed as mean \pm SEM. Differences between the two groups were tested for significance using the *t*-test for unpaired data and were considered statistically significant when $P < 0.05$.

Results

According to the Glasgow Outcome Scale, four of the 11 patients recovered without obvious neurological sequelae. Of the remainders, one was neurologically

Table 2. MAP, PaCO₂, C(av) DO₂, CBFE, and EEG before and during Barbiturate in the Nonrecovery Group

Patient number	Stage	MAP (mm Hg)	PaCO ₂ (mm Hg)	CaO ₂ (vol%)	CvO ₂ (vol%)	C(av) DO ₂	CBFE	Difference	EEG
1	B	90	31	21.0	10.9	10.1	10	17	Flat
	D	73	35	14.7	11.0	3.7	27		Burst & suppression
2	B	87	27	15.3	8.2	7.3	14	3	Slow wave & high voltage
	D	73	32	16.2	10.4	5.8	17		Flat
3	B	73	46	16.9	13.3	3.6	28	-14	Flat
	D	90	48	19.2	11.8	7.4	14		Flat
4	B	120	30	19.8	10.3	9.5	11	2	Slow wave & high voltage
	D	90	29	16.8	9.2	7.6	13		Fast wave
8	B	83	36	18.3	15.7	2.6	39	-11	Spike & slow wave
	D	77	38	18.0	14.3	3.7	27		Burst & suppression
10	B	97	37	20.3	9.8	10.5	10	4	Slow wave
	D	97	33	16.4	9.2	7.2	14		Burst & suppression
11	B	100	36	18.7	14.5	4.2	24	-1	Slow wave & low voltage
	D	83	38	21.7	17.4	4.3	23		Flat
mean ± SEM	B	93	35	18.6	11.8	6.8	19	0.2	
		6	2	0.7	1.0	1.3	4	4.0	
	D	83	36	17.6	11.9	5.7	10		
		4	2	0.9	1.1	0.7	2		

Abbreviations: B, before barbiturate; D, during barbiturate; MAP, mean arterial pressure; difference, difference in CBFE between, before, and during barbiturate therapy.

severely disabled, two were vegetative, and four died. The recovery group included the four patients with good recovery; the nonrecovery group included the seven patients who had neurological sequelae or died. Tables 2 and 3 summarize the mean arterial pressure (MAP), arterial carbon dioxide (PaCO₂), CvO₂, C(av)DO₂, CBFE, and EEG findings before and during barbiturate therapy. All patients were normocarbic during the study.

The mean value of C(av)DO₂ before barbiturate administration was 2.6 ± 0.2 vol% in those who recovered and 6.8 ± 1.3 vol% in those who did not recover. The remarkably low C(av)DO₂ level in the recovery group was significantly lower than that in the nonrecovery group. The barbiturate administration significantly increased C(av)DO₂ in recovery group to 8.1 ± 0.6 vol% from 2.6 ± 0.2 vol% but had no significant effect in the nonrecovery group, where C(av)DO₂ was 6.8 ± 1.3 vol% before and 5.7 ± 0.7 vol% after initiation of barbiturate therapy. The changes in CBFE were similar but opposite to those of C(av)DO₂. The decrease in CBFE in the recovery group associated with barbiturate therapy was more than 20 ml blood/ml O₂. All recovered patients showed some EEG activity before the administration of barbiturate, and their EEGs showed "burst and suppression" with a flat period of 3–100 sec after the administration of barbiturate. Barbiturate administration was not as-

sociated with complications in our patients except for mild hypotension that readily responded to the infusion of dopamine.

Discussion

Administration of large doses of barbiturate has been suggested treatment for various brain injuries, including anoxic encephalopathy (8), Reye's syndrome (9), and brain trauma (1). The continuous monitoring of ICP is essential as a guide to the management of such patients, but it is not as easily performed as EEG monitoring because of the need for special equipment.

We examined whether the CBFE could be used to evaluate the effect of barbiturate on cerebral ischemic injuries as a bedside monitor. CBFE may be useful in determining the relative degree of global cerebral ischemia (10). Because the CBFE is the ratio between CBF and CMRO₂, subnormal values suggest the presence of flow insufficient for metabolic needs. Conversely, an abnormally high value of CBFE reflects a flow greater than that needed for metabolism. The adequacy of the cerebral oxygen supply thus may be estimated from the ratio of flow to metabolic rate. The ratio of CBF/CMRO₂, CBFE, is equal to $1/C(av)DO_2$, which can be determined without measurement of either CBF or CMRO₂. Where CMRO₂ is stable, for example, CBFE has been used to estimate relative changes in

Table 3. MAP, PaCO₂, C(av) DO₂, CBFE, before and during Barbiturate in the Recovery Group

Patient number	Stage	MAP (mm Hg)	PaCO ₂ (mm Hg)	CaO ₂ (vol%)	CvO ₂ (vol%)	C(av) DO ₂	CBFE	Difference	EEG
5	B	77	33	17.2	15.0	2.2	46	-35	Slow wave
	D	83	31	15.9	6.6	9.3	11		Burst & suppression
6	B	117	30	14.8	12.3	2.5	40	-26	Slow wave & high voltage
	D	103	34	17.7	10.6	7.1	14		Burst & suppression
7	B	90	29	19.8	16.9	2.9	35	-23	Slow wave & high voltage
	D	80	32	19.2	10.5	8.7	12		Burst & suppression
9	B	93	36	20.1	17.3	2.8	36	-22	Spike & fast wave
	D	87	40	19.8	12.6	7.2	14		Burst & suppression
mean ± SEM	B	94	32	18.0	15.4	2.6	39	-26	
		8	2	1.3	1.1	0.2	3	3	
	D	88	34	18.2	10.1	8.1 ^a	13 ^a		
		5	2	0.9	1.2	0.6	1		

Abbreviations same as for Table 2.

^aSignificant from before barbiturate ($P < 0.05$)

CBF (6). The CMRO₂ has been found to be reduced in patients in coma to 1.0–2.0 ml·100g⁻¹·min⁻¹ (11–15). Tabaddor et al. (12) measured CBF and CMRO₂ in patients with head injuries and showed that C(av)DO₂ is about 2.0 vol%, i.e., CBFE is about 50 ml blood/ml O₂, when CMRO₂ is below 2.0 ml·100⁻¹g·min⁻¹. Their data show that a low C(av)DO₂ or a high CBFE indicates a low CMRO₂. By measurement of CBF and CMRO₂, Beckstead et al. (16) confirmed that jugular venous oxygen content increased, while C(av)DO₂ decreased, indicating a progressive increase in the ratio of CBF to metabolism and an increase in CBFE.

In our study we observed that a high CBFE before barbiturate therapy significantly decreased to normal values after the administration of barbiturate in patients in the recovery group. On the other hand, significant changes in CBFE were not observed in patients in the nonrecovery group, after the administration of barbiturate. All of the patients in the recovery group showed relatively high CBFE or low C(av)DO₂ values that improved during barbiturate therapy. However, patients in the nonrecovery group showed relatively low CBFE or high C(av)DO₂ values that did not change during barbiturate therapy. One patient (number 8) in the nonrecovery group did have a CBFE or C(av)DO₂ that was similar to those seen in the recovery group. She was a patient with severe brain edema after neurosurgery for craniopharyngioma, as was shown by computerized tomography scan at the first postoperative day, despite mannitol and steroids immediately started after surgery. After the administration of barbiturate, the CBFE in this patient showed no change, as in other patients in the nonrecovery group. This suggests that in this patient the

response of the cerebral vasculature to barbiturates had been already lost.

Most patients in coma already have reduced cerebral metabolism, and it is questionable whether barbiturate will augment this reduction (2). Michenfelder (17) found that CMRO₂ decreased progressively until the EEG became isoelectric, indicating cessation of cortical function, in dogs given a continuous thiopental infusion, and additional thiopental had no further effects on CMRO₂. Therefore, in this study, the reduction in CBFE with barbiturate may be due to the increase in cerebrovascular resistance, which is attributable to CBF rather than to reduction in CMRO₂. The results of our study suggest that barbiturates may affect cerebral hemodynamics, not metabolism, and that CBFE may be useful during barbiturate therapy.

In conclusion, we found that decreases in CBFE associated with barbiturate therapy were accompanied by complete neurological recovery from cerebral ischemic insults, whereas the absence of changes in CBFE during barbiturate therapy was accompanied by poor prognoses. Barbiturate therapy is useful in patients who respond to barbiturate therapy by changes in cerebral vascular function and/or cerebral metabolism.

References

1. Marshall LF, Smith RW, Shapiro HM. The outcome with aggressive treatment in severe head injuries. Part II: Acute and chronic barbiturate administration in the management of head injury. *J Neurosurg* 1979;50:26–30.
2. Rockoff MA, Marshall LF, Shapiro HM. High-dose barbiturate therapy in human: a clinical review of 60 patients. *Ann Neurol* 1979;6:194–9.

3. Teasdale G, Jennett B. Assessment of coma and impaired consciousness. A practical scale. *Lancet* 1974;ii:81-3.
4. Yonei A, Nonoue T, Sari A. Real-time ultrasonic guidance for percutaneous puncture of the internal jugular vein. *Anesthesiology*, in press.
5. Ishikawa T, Oshita S, Kumagai S, Okuda Y. Measurement of oxygen content in the blood: comparison of five different methods. *Jpn J Anesthesiology* 1977;26:162-7.
6. Smith AL, Wollman H. Cerebral blood flow and metabolism: effects of anesthetic drugs and techniques. *Anesthesiology* 1972;36:378-400.
7. Jennett B, Bond M. Assessment of outcome after severe brain damage. Practical scale. *Lancet* 1975;i:480-4.
8. Breivik H, Safer P, Sands P, et al. Clinical feasibility trials of barbiturate therapy after cardiac arrest. *Crit Care Med* 1987;6:254-69.
9. Marshall LF, Shapiro HM, Rausher A, et al. Pentobarbital therapy for intracranial hypertension in metabolic coma—Reye's syndrome. *Crit Care Med* 1978;6:1-5.
10. Bruce DA, Gennarelli TA, Langfitt TW. Resuscitation from coma due to head injury. *Crit Care Med* 1978;6:254-69.
11. Shalit MN, Beller AJ, Feinsod M, Drapkin AJ, Cotev S. The blood flow and oxygen consumption of the dying brain. *Neurology* 1970;20:740-8.
12. Tabaddor K, Bhushan C, Pevsner PH, Walker AE. Prognostic value of cerebral blood flow (CBF) and cerebral metabolic rate of oxygen (CMRO₂) in acute head trauma. *J Trauma* 1972;12:1053-5.
13. Bruce DA, Langfitt TW, Miller JD, et al. Regional cerebral blood flow, intracranial pressure, and brain metabolism in comatose patients. *J Neurosurg* 1973;38:131-44.
14. Brodersen P, Jorgensen EO. Cerebral blood flow and oxygen uptake, and cerebrospinal fluid biochemistry in severe coma. *J Neurol Neurosurg Psychiatry* 1974;37:384-91.
15. Cotev S, Shalit M. Effects of diazepam on cerebral blood flow and oxygen uptake after head injury. *Anesthesiology* 1975;43:117-22.
16. Beckstead JE, Tweed WA, Lee J, MacKeen WL. Cerebral blood flow and metabolism in man following cardiac arrest. *Stroke* 1978;9:579-72.
17. Michenfelder JD. The interdependency of cerebral function and metabolic effects following massive doses of thiopental in the dog. *Anesthesiology* 1974;41:231-6.

Special Article

Spinal Subarachnoid Hematoma after Lumbar Puncture and Heparinization:

A Case Report, Review of the Literature, and Discussion of Anesthetic Implications

Eddie L. Owens, MD, Gregory W. Kasten, MD, and Eugene A. Hessel II, MD

A case is presented in which a patient received an uneventful general anesthetic for repair of a ventral hernia. In the postoperative period he developed respiratory and neurologic dysfunctions, which were evaluated by CT scan of the head, ventilation-perfusion scan of the lungs, and lumbar puncture. The patient was found to have pulmonary embolization with consequent hypoxemia, and his neurologic dysfunction was secondary to the latter. Heparin therapy was begun, and approximately 16 hr later the patient developed paraplegia. A laminectomy was performed, revealing a subarachnoid hematoma, which was evacuated, but postoperatively the patient remained paraparetic. Other cases involving lumbar puncture and spinal hematoma, with and without impairment of the hemostatic mechanism, are reviewed. Also discussed are cases in which spinal and epidural anesthesia have been given with subsequent heparinization without complication. Factors that appear to reduce the risk of hematoma formation after lumbar puncture are presented.

Case Report

The administration of spinal anesthesia to a patient who is receiving anticoagulant therapy or who will receive such therapy during the course of a surgical procedure remains controversial. However, few re-

ports or experimental data substantiate the possibility that such an anesthetic technique might be hazardous. The following case report illustrates potential problems in such a patient.

A 70-yr-old male was admitted to the hospital for elective repair of an epigastric incisional hernia. Surgical history included bilateral inguinal hernia repairs, a splenectomy, and a nephrolithotomy, all treated without complications. Medical history included a 15-yr history of hypertension, and paroxysmal supraventricular tachyarrhythmias since his teenage years. The patient smoked only a pipe; he had degenerative joint disease of the lumbar spine. The patient was receiving furosemide, digoxin, verapamil, allopurinol, potassium, and multivitamins.

On physical examination the patient was afebrile, blood pressure was 130/94 mm Hg, pulse rate was 80/min, respirations were 16/min, and he weighed 87 kg. The cardiac rhythm was intermittently irregular; a grade 2/6 systolic murmur was heard and a trace of edema was noted at both ankles.

Preoperative laboratory values for prothrombin time, partial thromboplastin time, and platelet count were normal. Chest x-ray was normal, and the electrocardiogram showed a sinus bradycardia and nonspecific ST-T wave changes.

The patient was taken to the operating room where the hernia was repaired under an uneventful isoflurane-nitrous oxide-oxygen anesthesia. The evening of surgery was also uneventful, with the patient receiving only the usual amounts of postoperative analgesics.

At about 10:30 AM on the first postoperative day, the patient suddenly developed right hemiparesis,

Received from the Veterans Administration Medical Center and the University of Kentucky Medical Center, Lexington, Kentucky. Accepted for publication June 2, 1986.

Address correspondence to Dr. Owens, 128 CDD, Veterans Administration Medical Center, Lexington, KY 40511.

Table 1. Spinal Hematoma after Attempted Spinal Anesthesia

Author (s)	Reference	Year	Difficult tap	Bloody tap	Anticoagulant coagulopathy	Neurologic recovery	Remarks
Bonica	(11)	1953	N/R	Yes	None	N/R	Prolonged bleeding time
King and Glas	(12)	1959	No	Yes	None	Good	Laminectomy-pulmonary embolus
Lerner et al.	(13)	1973	Yes	Yes	None	Poor	Laminectomy
Rengachary and Murphy	(14)	1974	Yes	No	None	60%*	Laminectomy
Greensite and Katz	(15)	1980	Yes	Yes	None	Poor	Continuous SAB-aspirin-laminectomy
Mayumi and Dohi	(16)	1983	Yes	No	None	Poor	Antiplatelet drugs-laminectomy

Abbreviation: N/R, not reported by author.

*Moderate

expressive aphasia, right sided clonus, and evidence of right seventh cranial nerve dysfunction. The patient also appeared to be having respiratory difficulty. Arterial blood gases measured while the patient breathed room air revealed a PaO_2 of 31 torr, a PaCO_2 of 33 torr and a pH of 7.44. A chest x-ray showed mild elevation of the right hemidiaphragm and a small amount of discoid atelectasis at the right lung base. Diffuse ST and T wave changes were present on the electrocardiogram.

A CT scan of the head was normal and a ventilation-perfusion scan of the lungs revealed numerous segmental and subsegmental defects consistent with multiple pulmonary emboli.

A lumbar puncture was performed at 5:00 PM to rule out intracranial hemorrhage as a cause of the neurologic dysfunction. The procedure was technically difficult, but ultimately yielded clear cerebrospinal fluid (CSF). The second tube contained 1450 red blood cells (RBC) per cubic milliliter, and the fourth tube contained 370 RBC.

The diagnostic impression was that the cerebral ischemic event was nonhemorrhagic. At 7:15 PM the patient was systemically heparinized with 5000 U of heparin intravenously, followed by an infusion of 1000 U/hr. The therapeutic goal was to maintain the partial thromboplastin time at 2-2.5 times control. Early values were found to be greater than 120 sec with a control value of 24 sec.

That evening the patient's clinical condition improved. Patient's PaO_2 was maintained at about 100 torr by the administration of mask oxygen. Over the next few hours, the aphasia began clearing, and the patient regained the ability to move his right arm.

At midnight the patient began having severe low back pain that continued over the next several hours. At 11:00 AM the patient developed bilateral lower extremity paralysis and sensory anesthesia to pinprick below the level of L-1. The impression of the consulting neurosurgeon was that the patient had de-

veloped spinal cord compression from a hematoma following lumbar puncture and subsequent anticoagulation.

At 3:00 PM the patient was returned to the operating room where he underwent back exploration under isoflurane-nitrous oxide-oxygen anesthesia.

As the lumbar dura was exposed, the surgeon found a small clot extruding from the dura at the L3-4 level. The dura was tense and exhibited a bluish discoloration. As the meninges were opened, a clot and a large amount of bloody cerebrospinal fluid were extruded under pressure. After additional clots were irrigated from the subarachnoid space, no active bleeding was noted (i.e., the source of the hematoma) and the incision was closed.

Recovery from the anesthetic and the operation was uneventful, but the patient failed to regain any significant amount of neurologic function after the operation.

Discussion

Neurologic dysfunction after bleeding into the spinal canal (i.e., epidural, subdural, or subarachnoid hemorrhage) is rare. It has been reported in a variety of clinical situations: spontaneously (1); in association with anticoagulant (2) or antiplatelet therapy (3); with vascular abnormalities (4); with neoplastic disease in the spinal canal (5); and with the introduction of a needle into the epidural or subarachnoid space.

The incidence of such complications in association with spinal anesthesia is unknown. Although obviously related, to limit the scope of this review we have elected to confine this discussion to lumbar puncture and spinal anesthesia and to exclude discussion of epidural anesthesia.

Not a single case of spinal hematoma was reported in the combined series of Vandam and Dripps (6), Moore and Bridenbaugh (7), Phillips et al. (8), and Sadove et al. (9), totaling more than 50,000 spinal

Table 2. Hematoma after Diagnostic or Therapeutic Lumbar Puncture

Author	Reference	Year	Difficult tap	Bloody tap	Anticoagulant coagulopathy	Neurologic recovery	Remarks
Cooke	(17)	1911	No	Yes	None	Died	Tuberculous meningitis—autopsy showed hematoma
Hammes	(18)	1920	No	N/R	None	Good	Presumed hematoma—no surgery
Courtin	(19)	1952	N/R	N/R	None	Died	CNS syphilis—laminectomy
Wolcott	(20)	1970	No	No	Platelets, 1000	Died	Leukemia
DeAngelis	(21)	1972	No	No	Coumadin	Died	Pulmonary embolus
Edleson et al. #1	(22)	1974	Yes	N/R	Platelets, 44,000	Died	Leukemia
Edleson et al. #2	(22)	1974	No	No	Platelets, 25,000	Good	Clinical diagnosis—no surgery
Edleson et al. #3	(22)	1974	N/R	No	Platelets, 3000	Died	No CSF obtained—diagnosis ITP
Edleson et al. #4	(22)	1974	No	No	Platelets, 19,000	Died	Leukemia—no surgery
Edleson et al. #5	(22)	1974	Yes	No	Platelets, 37,000	Died	Lung cancer—no surgery
Edleson et al. #6	(22)	1974	Yes	Yes	Platelets, 15,000	Died	Leukemia—five LP attempts
Edleson et al. #7	(22)	1974	Yes	N/R	Platelets, 18,000	Died	Leukemia—multiple LP attempts
Edleson et al. #8	(22)	1974	Yes	Yes	Platelets, 10,000	Died	Lymphosarcoma
Kirkpatrick and Goodman	(23)	1975	No	No	None	Good	Laminectomy
Messer et al.	(24)	1976	No	No	Heparin	Good	Gradual recovery—no surgery
Senelick et al.	(25)	1976	No	Yes	Heparin	Good	Laminectomy—CVA vs TIA
Sadjadpour	(26)	1977	Yes	No	Heparin/Coumadin	Moderate	Laminectomy—pulmonary embolism CVA
Diaz et al.	(27)	1978	Yes	No	Heparin	Good	TIA—laminectomy
Laglia et al.	(28)	1978	No	No	Coagulopathy	Poor	Laminectomy—cirrhosis/sepsis
Brem et al. #1	(29)	1981	Yes	Yes	Heparin	Partial	Laminectomy
Brem et al. #2	(29)	1981	No	No	Heparin	Moderate	TIA—laminectomy
Brem et al. #3	(29)	1981	N/R	N/R	Heparin	Partial	No surgery—partial recovery
Ruff and Dougherty #1	(30)	1981	N/R	Yes	Heparin/Coumadin	Good	Laminectomy
Ruff and Dougherty #2	(30)	1981	N/R	Yes	Heparin/Coumadin	Good	Laminectomy
Ruff and Dougherty #3	(30)	1981	N/R	Yes	Heparin/Coumadin	Good	Laminectomy
Ruff and Dougherty #4	(30)	1981	N/R	Yes	Heparin/Coumadin	N/R	Hematoma removed with needle
Ruff and Dougherty #5	(30)	1981	N/R	No	Heparin/Coumadin	Poor	Refused surgery

Abbreviations: N/R, not reported by author; CNS, central nervous system; CSF, cerebrospinal fluid; ITP, idiopathic thrombocytopenic purpura; LP, lumbar puncture; CVA, cerebrovascular accident; TIA, transient ischemia attack.

anesthetics. In Greene's review of neurologic sequelae of spinal anesthesia, no cases of spinal hematoma were cited (10).

However, with the exception of Phillips et al., who reported a 3% incidence of bloody taps and a 6% incidence of multiple lumbar puncture attempts, the occurrence of predisposing factors was not mentioned by these authors. Other predisposing factors include blood dyscrasias, thrombocytopenia, antiplatelet therapy, anticoagulation, and difficult or traumatic lumbar puncture.

In the literature in English, we have found 33 cases of spinal hematoma presenting with neurologic dysfunction after attempted lumbar puncture (LP). In six cases (Table 1) the LP involved the administration of an anesthetic (11–16), and in 27 cases (Table 2) the LP was for diagnostic or therapeutic purposes (17–30). Twelve of the hematomas were subarachnoid, six were subdural, six were both subarachnoid and subdural, and seven were epidural. In two patients the site of the hematoma was not specified.

Thirteen of the 33 patients had received anticoagulants: heparin in six, coumadin in one, and heparin followed by coumadin in six. Another patient had prolonged bleeding time, for reasons not reported; yet another patient had a coagulopathy from endstage liver disease. Only two of the patients were given anticoagulants before lumbar puncture.

Nine of the 33 patients had thrombocytopenia, with a platelet count less than 50,000/ml. Another patient was being treated with antiplatelet therapy before the LP and still another received aspirin beginning 4 hr after the LP. Thus, in 26 of the 33 patients (79%), the hematomas associated with lumbar puncture occurred in patients with evidence of hemostatic abnormality.

Twelve of the lumbar punctures were described as difficult, and five of these 12 were bloody; in another eight patients the lumbar puncture was not reported to be difficult, but nonetheless blood was obtained from the LP needle. In the remaining 13 patients the lumbar puncture was neither difficult nor bloody.

Fifteen of the 33 patients (45%) had partial or good recovery of neurologic function. Eleven of these patients had laminectomies, three patients recovered progressively without surgery, and the other patient had partial recovery without any intervention.

Ten of the patients expired without surgery. The usual cause of death was coexisting disease (leukemia, sepsis, cerebrovascular accident, pulmonary embolus) rather than a direct result of the spinal hematoma (e.g., respiratory embarrassment caused by cervicothoracic involvement by the hematoma). Five of the 16 patients who had laminectomies had little or no return of neurologic function. One patient refused surgery and remained paraplegic. In two other nonoperated patients the outcome was not reported.

Of the six cases in which the LP involved the administration of an anesthetic, three were converted to general anesthetics after multiple attempts at lumbar puncture yielded bloody CSF (13) or no CSF (14,16). Another case involved an attempted epidural anesthetic at the L2-3 interspace associated with gross blood dripping from the needle. Reinsertion of the epidural needle an interspace lower resulted in the free flow of clear CSF, and the anesthetic technique was converted to continuous spinal anesthesia (15). In yet another case, the LP apparently was not difficult; bloody fluid was obtained initially, but it cleared shortly thereafter (12). In the remaining case no difficulties were reported (11). Thus, in five of the six, LP was difficult (unsuccessful) or bloody.

Of six patients who had anesthetics, none received anticoagulants, although one was on antiplatelet therapy preoperatively (16). Postoperatively, one patient received salicylates (15), and another was found to have a prolonged bleeding time (11). Another patient had hepatic cirrhosis, but no bleeding or clotting abnormalities were reported (12). In the two remaining patients no predisposing factors could be identified (13,14).

Brem et al. (29) reported two cases of subarachnoid hematoma in patients with transient ischemic attacks undergoing diagnostic LP with subsequent heparinization. In their retrospective review of 167 patients who had lumbar puncture followed by heparinization, eight patients had severe lumbar and radicular pain for greater than two days, and three of the eight became paraplegic. The doses of heparin used and subsequent clotting studies were not reported.

In a retrospective study, Ruff and Dougherty (30) reported a series of 342 patients who received diagnostic lumbar puncture in evaluation of acute cerebral ischemic attacks. All were then given heparin, and five of these subsequently became paraplegic. A second group of 342 patients with cerebral ischemia,

meningitis, or multiple sclerosis underwent lumbar puncture without heparinization and no cases of paraplegia occurred. Eighteen patients in the heparinized group also developed severe back or lumbosacral radicular pain lasting greater than 48 hr. Of these, seven died from unrelated causes and at autopsy one had a chronic epidural hematoma and one had an organized subdural hematoma. Ruff and Dougherty identified a bloody tap, institution of heparin within 1 hr, and aspirin therapy at the time of the LP as being risk factors in the development of major complications in patients given heparin. The amounts of heparin used and resulting clotting studies were not reported.

Rao and El-Etr (31) reported on 3164 patients who had continuous epidural anesthesia and 847 patients who had continuous spinal anesthesia for elective lower extremity vascular surgery. None of the patients were given anticoagulants before the LP. If blood was aspirated at the time of catheter insertion, the case was cancelled and rescheduled under general anesthesia for the next day. About 1 hr after institution of the regional anesthetic, heparin was given intravenously in 500 U increments to maintain the activated clotting time (ACT) at approximately twice baseline (average requirement 2600 U). The heparin dose was repeated every 6 hr. The subarachnoid or epidural catheter was left in place for 24 hr to facilitate analgesia and was removed 1 hr before a scheduled maintenance heparin dose. No patients developed signs of subarachnoid or epidural hematoma.

Matthews and Abrams (32) reported on 40 patients undergoing open heart surgery in whom the main analgesic was intrathecal morphine (1.5-4.0 mg) administered with a 20-25-gauge needle shortly after induction of general anesthesia. The minimum interval between lumbar puncture and heparinization was 50 min. No cases of spinal hematoma occurred; however, the amounts of heparin administered and the incidence of traumatic lumbar punctures were not reported.

Many anesthesiologists would be reluctant to perform lumbar puncture in a patient already on anticoagulants. It is interesting to note that Odoom and Sih (33) report 1000 epidural anesthetics in 950 patients receiving oral anticoagulants at the time of epidural catheter placement. All patients were then heparinized for vascular surgery; none developed neurologic dysfunction. Excluded from their study were patients with neurologic disease, infection at the puncture site, blood dyscrasias (including thrombocytopenia), prior heparinization, and thrombotest below 10%. Intraoperative heparin administration was carefully monitored, and the dose was quite low.

An issue of great concern to anesthesiologists is

the management of patients receiving "minidose" heparin preoperatively for thromboembolism prophylaxis. To our knowledge, no case reports have been published demonstrating neurologic complications after administration of an epidural or spinal anesthetic to a patient who received low-dose heparin preoperatively; however, no data are available to document the safety of this procedure. Murphy (34) states that the safety of epidural or spinal anesthesia after low-dose heparin is controversial, and that spinal or epidural anesthesia is probably not safe if the heparin results in abnormal coagulation studies.

A great deal of the uncertainty about whether to administer regional anesthesia after low-dose heparin relates to the unpredictability of the coagulation response to heparin. The investigation by Cooke et al. (35) revealed that approximately 50% of patients receiving 5000 U of heparin subcutaneously had therapeutic rather than prophylactic blood levels of heparin for up to 4 hr. Several factors might explain the unpredictable response to heparin: 1) the molecular heterogeneity of different species of heparin; 2) individual variation in response to heparin; 3) the level and binding affinity of antithrombin III; 4) drug interactions with heparin; and 5) dose-dependency of heparin half-life (36,37).

At this time it does not appear possible to predict an individual patient's response to heparin. Therefore formulation of a blanket recommendation to cover the administration of regional anesthesia in patients receiving low-dose heparin is difficult.

Lumbar puncture, including subarachnoid block, is usually free of serious hemorrhagic complications, as attested by the absence of such complications in several combined series involving over 50,000 spinal anesthetics (6-9). On the other hand, that such complications can occur is confirmed by the 33 previously reported cases, as well as the subject of this case report. The role of anticoagulation or some other abnormality of hemostasis in this complication is suggested by the approximately 48 spinal hematomas associated with anticoagulation or other clotting abnormalities in the absence of LP or other introductions of needles into the spine (38,39), and that anticoagulation, coagulopathy, thrombocytopenia, or antiplatelet therapy were present in at least 26 (79%) of the spinal hematomas that have been reported after lumbar puncture. On the other hand, hematomas can follow lumbar puncture even in the absence of known disturbances of hemostasis, and the two series of patients presented by Matthews and Abrams (32) and Rao and El-Etr (31) indicate that spinal anesthesia can be accomplished safely even when followed by heparinization.

How can all of these data, some of which are conflicting, be reconciled? Particularly troubling are the combined series of 509 diagnostic lumbar punctures followed by systemic anticoagulation in which 8 (1.6%) serious spinal hematomas were encountered (29,30). This frequency of complications contrasts with the absence of such complications in the two combined series of 887 spinal anesthetics that were followed by systemic heparinization (31,32). Possible factors that might explain these different outcomes include 1) the skill with which the LP was done, 2) the size of the needle used for LP (but in Rao and El-Etr's series 17-gauge Tuohy needles were used), 3) the dose and duration of heparinization (but in Matthews and Abrams series sufficient heparin for cardiopulmonary bypass was administered). Alternatively, the differing results may simply represent the statistically expected variable incidence of a relatively infrequent event. As pointed out by Hanley and Lippman-Hand (40), studies that find zero events do not necessarily mean that the risk is zero in the whole population. In a study with a sample size of 40 (e.g., Matthews and Abrams) with zero events, the maximum risk (with 95% confidence) could still be as high as 7.5%, and with a sample size of 847 (e.g., Rao and El-Etr's study) it could be as high as 0.35%.

Based on available information, and until further data are presented, we believe the following recommendations are appropriate:

1. It is generally agreed, although not proven, that LP is potentially dangerous and, in the absence of extraordinary indications, should be avoided in patients who have received anticoagulants or who have a known coagulopathy or significant thrombocytopenia (platelet count less than 100,000?).
2. The risk attending LP in patients receiving antiplatelet drugs or aspirin is less clear, but concern is generated by cases such as those presented by Mayumi and Dohi (16) and Greensite and Katz (15).
3. The performance of LP on patients given minidose heparin has raised concern, but is apparently being done in some institutions. Unfortunately, no reported cases or series document either its safety or its risk. Until such data become available it seems prudent to avoid spinal anesthesia in patients given minidose heparin preoperatively unless spinal anesthesia is strongly indicated over other anesthetic methods. Furthermore, if subarachnoid block is elected in such a patient, it seems advisable to assure that the patient does not have evidence of systemic heparinization (i.e., the activated clotting time or partial thromboplastin time is normal) im-

mediately prior to performing the LP. Again, the need and safety of such an approach are not proven.

4. The safety of LP that is to be followed by anticoagulation is likewise unresolved because of conflicting data. The existing data do not exclude a possible risk of serious spinal hemorrhage as high as 0.35%. If spinal anesthesia is selected in such a patient, then anesthesia should be accomplished as atraumatically as possible with a small needle. If the LP is traumatic or bloody, further caution is advised. The subsequent heparinization should be controlled (e.g., with activated clotting time or partial thromboplastin time), with the smallest dose and shortest duration used that is compatible with the therapeutic objectives. One should be particularly cautious of such a procedure in a patient who is also taking aspirin or other antiplatelet agents.
5. Whenever spinal anesthesia is performed in any of the above circumstances, it is especially important to monitor the patient frequently and closely during the postoperative period, to institute promptly appropriate diagnostic studies if any signs or symptoms suggesting spinal hematoma occur, and to initiate expeditious surgical intervention if a spinal hematoma is likely. Such actions should minimize the incidence of permanent serious neurologic sequelae.

In summary, a case is presented in which a patient underwent LP followed within 2.25 hr by systemic heparinization, who developed paraplegia secondary to subarachnoid hematoma despite a laminectomy. Although such an occurrence is rare, risk appears to be involved in the performance of lumbar puncture on a patient whose hemostatic mechanism is impaired. Careful monitoring of the extent of anticoagulation, screening of patients for thrombocytopenia, antiplatelet therapy, and preexisting coagulation disorders may reduce the risk involved.

Future investigations are needed to define the risk of neurologic damage from spinal hematoma following spinal anesthesia in patients receiving minidose heparin preoperatively.

References

1. Costabile G, Husag L, Probst C. Spinal epidural hematoma. *Surg Neurol* 1984;21:489-92.
2. Bamford CR. Spinal epidural hematoma due to heparin. *Arch Neurol* 1978;35:693-4.
3. Locke GE, Giorgio AJ, Biggers SL, Johnson AP, Salem F. Acute spinal epidural hematoma secondary to aspirin-induced prolonged bleeding. *Surg Neurol* 1976;5:293-5.
4. Aminoff MJ, Logue V. The prognosis of patients with vascular malformations. *Brain* 1974;97:211-8.
5. Prieto A, Cantu RC. Spinal subarachnoid hemorrhage associated with neurofibroma of the cauda equina. *J Neurosurg* 1968;27:63-9.
6. Vandam LD, Dripps RD. Long term follow-up of patients who received 10,098 spinal anesthetics. *JAMA* 1960;172:1483-87.
7. Moore DC, Bridenbaugh LD. Spinal (subarachnoid) block. A review of 11,574 cases. *JAMA* 1966;195:907-12.
8. Phillips OC, Ebner H, Nelson AT, Black MH. Neurologic complications following spinal anesthesia with lidocaine: a prospective review of 10,440 cases. *Anesthesiology* 1969;30:284-9.
9. Sadove MS, Levin MJ, Rant-Sejdinaj I. Neurological complications of spinal anesthesia. *Can Anaesth Soc J* 1961;8:405-16.
10. Greene NM. Neurological sequelae of spinal anesthesia. *Anesthesiology* 1961;22:682-98.
11. Bonica JJ. The management of pain. Philadelphia: Lea and Febiger, 1953:493.
12. King OJ, Glas WW. Spinal subarachnoid hemorrhage following lumbar puncture. *Arch Surg* 1960;80:574-7.
13. Lerner SM, Gutterman P, Jenkins F. Epidural hematoma and paraplegia after numerous lumbar punctures. *Anesthesiology* 1973;39:550-1.
14. Rengachary SS, Murphy D. Subarachnoid hematoma following lumbar puncture causing compression of the cauda equina: case report. *J Neurosurg* 1974;41:252-4.
15. Greensite FS, Katz J. Spinal subdural hematoma associated with attempted epidural anesthesia and subsequent continuous spinal anesthesia. *Anesth Analg* 1980;59:72-3.
16. Mayumi T, Dohi S. Spinal subarachnoid hematoma after lumbar puncture in a patient receiving antiplatelet therapy. *Anesth Analg* 1983;62:777-9.
17. Cooke JV. Hemorrhage into the cauda equina following lumbar puncture. *Proc Path Soc Phila* 1911;14:104.
18. Hammes EM. Hemorrhage in the cauda equina secondary to lumbar puncture. *Arch Neurol Psychiat (Chicago)* 1920;3:595.
19. Courtin RF. Some practical aspects of lumbar puncture. *Postgrad Med* 1952;12:157-61.
20. Wolcott GJ, Grunnet ML, Lahey ME. Spinal subdural hematoma in a leukemic child. *J Pediatr* 1970;77:1060-2.
21. DeAngelis J. Hazards of subdural and epidural anesthesia during anticoagulant therapy: a case report and review. *Anesth Analg* 1972;51:676-9.
22. Edleson RN, Chernik NL, Posner JB. Spinal subdural hematomas complicating lumbar puncture. *Arch Neurol* 1974;31:134-7.
23. Kirkpatrick D, Goodman SJ. Combined subarachnoid and subdural hematoma following spinal puncture. *Surg Neurol* 1975;3:109-11.
24. Messer HD, Forshan VR, Brust JCM, Hughes JEO. Transient paraplegia from hematoma after lumbar puncture. *JAMA* 1976;235:529-30.
25. Senelick RC, Norwood CW, Cohen GH. Painless spinal epidural hematoma during anticoagulant therapy. *Neurology* 1976;26:213-5.
26. Sadjadpour K. Hazards of anticoagulation therapy shortly after lumbar puncture. *JAMA* 1977;237:1692-3.
27. Diaz FG, Yock DH, Rockswold GL. Spinal subarachnoid hematoma after lumbar puncture producing acute thoracic myelopathy: case report. *Neurosurgery* 1978;3:404-6.
28. Lagia AG, Eisenberg RL, Weinstein PR, Mani RL. Spinal epidural hematoma after lumbar puncture in liver disease. *Ann Intern Med* 1978;88:515-6.
29. Brem SS, Hafler DA, VanUitert RL, Ruff RL, Reichert WH. Spinal subarachnoid hematoma: a hazard of lumbar puncture resulting in reversible paraplegia. *N Engl J Med* 1981;303:1020-1.

30. Ruff RL, Dougherty JH. Complications of lumbar puncture followed by anticoagulation. *Stroke* 1981;12:879-81.
31. Rao TLK, El-Etr AA. Anticoagulation following placement of epidural and subarachnoid catheters: an evaluation of neurologic sequelae. *Anesthesiology* 1981;55:618-20.
32. Matthews ET, Abrams LD. Intrathecal morphine in open heart surgery. *Lancet* 1980;ii:543.
33. Odoom JA, Sih IL. Epidural analgesia and anticoagulant therapy. Experience with one thousand cases of continuous epidurals. *Anaesthesia* 1983;38:254-9.
34. Murphy TM. Spinal, Epidural, and Caudal Anesthesia. In: Miller RD, ed. *Anesthesia*. 2nd ed. New York: Churchill Livingstone, 1986:1061-111.
35. Cooke ED, Lloyd MJ, Bowcock SA, Pilcher MD. Monitoring during low-dose heparin prophylaxis. *N Engl J Med* 1976;294:293-4.
36. O'Reilly RA. Anticoagulant, antithrombotic, and thrombolytic drugs. In: Gillman AG, Goodman LS, Rall TW, Murad F, eds. *The pharmacologic basis of therapeutics*. 7th ed. New York: Macmillan, 1985:1338-59.
37. Mabry CD, Thompson BW, Read RC, Campbell GS. Activated clotting time monitoring of intraoperative heparinization: our experience and comparison of two techniques. *Surgery* 1981;90:889-95.
38. Bruyn GW, Bosma NJ. Spinal extradural hematomas. In: Vinken PJ, Bruyn GW, eds. *Handbook of clinical neurology* (Vol. 26). Amsterdam: North-Holland, 1976:1-30.
39. Edleson RN. Spinal subdural hematomas. In: Vinken PJ, Bruyn GW, eds. *Handbook of clinical neurology* (Vol. 26). Amsterdam: North-Holland, 1976:31-8.
40. Hanley JA, Lippman-Hand A. If nothing goes wrong, is everything all right?: interpreting zero numerators. *JAMA* 1983;249:1743-5.

Review Article

The Infant and the Myoneural Junction

Nishan G. Goudsouzian, MD, MS, and Frank G. Standaert, MD

Early investigations suggested that the neuromuscular (NM) unit was less developed in the newborn than in the adult. This assumption was based on limited observations in human infants (1,2) and animals (3,4), without careful evaluation of the cholinergic receptor. Recent work in animals, made possible by the newly developed techniques of α -bungarotoxin localization and patch clamping, has revealed several important differences between fetal and adult receptors (5-8). Although this new methodology is difficult to apply in humans, particularly small infants, it yields suggestive results. In addition, several indirect physiological and pharmacological studies in the human neonate have differentiated the behavior of the infant myoneural receptor from that of the adult (9-12).

In this article we review recent findings on the myoneural cholinergic receptor and myoneural function. We explore the importance of these new observations with respect to the human neonate and show how this new knowledge may affect the interpretation of the action of muscle relaxants in infants.

Properties of Acetylcholine Receptors

The acetylcholine (ACh) receptor is the molecular entity that possesses the binding sites and the ion channel for ACh through which the ACh response occurs. Anatomically the postsynaptic receptors for the cholinergic transmitter are located primarily at the crests of the junctional folds as part of the integral membrane protein. They photograph as discrete rings 8-9 nm in diameter with a central pit, looking rather like a donut. They protrude for about 5 nm into the

extracellular space and about 2 nm intracellularly (Fig. 1).

Structurally the nicotinic, cholinergic, postsynaptic receptor is a glycosylated polypeptide chain organized into units in a rosette shape with a central pit assumed to be the mouth of the channel across which ions travel. Each rosette has a molecular weight of about 250,000 daltons. Each is made up of five units, two of which are known as α units, and the others as β , γ , and δ units. The α units are identical, each weighing about 40,000 da; under experimental conditions each α unit binds one α -bungarotoxin molecule and at least one ACh molecule. The β , γ , and δ units are 50,000, 60,000, and 65,000 da respectively (Fig. 1) (13-16).

The characterization and identification of acetylcholine receptor (AChR) properties were made possible by the discovery of the snake venom α -bungarotoxin, a polypeptide that binds specifically and almost irreversibly to the nicotinic receptors on skeletal muscles (17,18). This toxin competes with cholinergic agonists and antagonists for the same binding sites as ACh. Its experimental use demonstrates that the AChRs in mature animals are localized and the binding sites tightly packed (up to 20,000/ μm^2) in the crests of the juxtaneural third of the folded postsynaptic surfaces just beneath the active zones (19-21). The deeper regions of the junctional cleft are practically devoid of receptors and along the normal muscle fiber a one thousand-fold decrease in receptor density occurs in the extrasynaptic membrane 200 μm away from the endplate (18).

In the resting state the transmitter ACh is spontaneously discharged in small amounts from the vesicles present in the presynaptic nerve ending, thus causing miniature endplate potentials. However, when a nerve is depolarized, Ca^{+2} traverses and enters the presynaptic area, as a result of which vesicles fuse with the presynaptic membrane and release large amounts of the ACh transmitter into the synaptic cleft.

Received from the Department of Anesthesiology, Harvard Medical School at the Massachusetts General Hospital, Boston, Massachusetts, and the Department of Pharmacology, Georgetown University School of Medicine and Dentistry, Washington DC. Accepted for publication May 1, 1986.

Address correspondence to Dr. Goudsouzian, Department of Anesthesia, Massachusetts General Hospital, Boston, MA 02114.

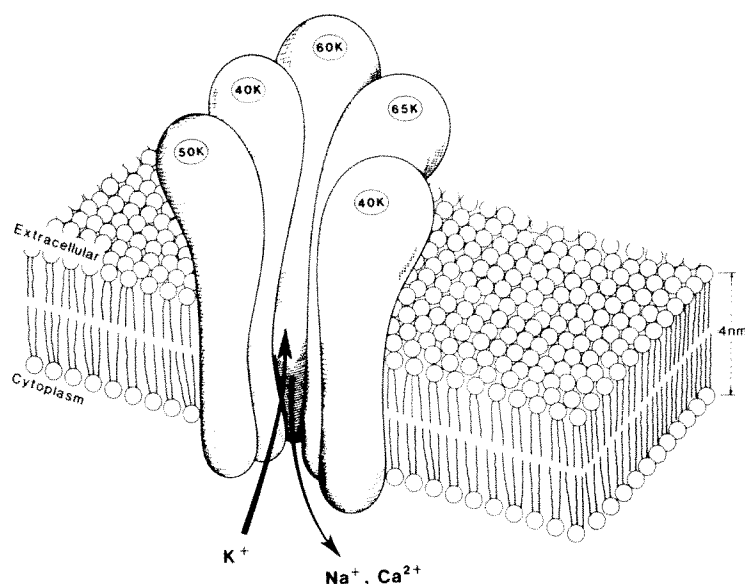


Figure 1. A diagrammatic representation of a postsynaptic acetylcholine receptor.

A nerve action potential usually releases about 200–500 quanta of ACh, each containing 2000–10,000 transmitter molecules. Within microseconds a portion of this released ACh binds to the receptors on the postsynaptic membrane changing their conformational shape and inducing the opening of discrete ion channels (22). Two ACh molecules must bind to the receptor before an ion channel may open.

There are about 10 million receptors in the entire endplate. Each quantum of released ACh transmitter is capable of generating about 1500 open channels in the postsynaptic membrane and causing an endplate current of about 4 nA at a resting potential of -80 mV. (A release of 200–300 quanta, or 400,000 to 2 million molecules of transmitter, will therefore result in the opening of between 250,000–500,000 ion channels with an endplate response between 400 to 800 nA.) A single channel is usually open for 1 msec, within which interval about 10,000 ions, mainly Na^+ and K^+ and to a lesser extent Ca^{+2} , can cross (18). With the opening of the ion channels an endplate potential is created that triggers a wave of depolarization and hence causes the muscle to contract. The receptor thus acts as a powerful amplifier converting the current carried by two ACh molecules to a current carried by many thousands of cations. Further, the receptor acts as a switch by opening and closing its ion channels, switching the current on and off as ACh molecules attach and detach.

The area of the ACh-binding sites of the α units is that in which the classic competition between cholinergic agonists and antagonists occurs. When both the α units are occupied by an agonist, the channel opens and ions flow. Conversely if either one, or both are

occupied by an antagonist no flow will occur. Muscle relaxants such as tubocurarine act by binding to either or both of the α units, thus preventing ACh from binding and opening the channel. This is a competitive antagonism and the outcome depends on the relative concentrations and the binding characteristics of the drug involved (23). This competitive antagonism is the most important effect of muscle relaxants in their action on the myoneural junction.

Another mechanism by which drugs affect NM transmission is channel blockade. Channel blockade occurs because the ion channel is much larger at the extracellular end than at the area where it crosses the membrane. Consequently, large molecules that enter the channel are unable to cross and thus act as a plug preventing the normal flow of ions through the channel tube. Because the flow of ions through the channel is impeded, depolarization and NM transmission do not occur. An important feature of open channel blockade is that it is use-dependent (6). Channels to be blocked must first be opened; hence channel blockade is amplified as more channels are opened in the presence of depolarizing muscle relaxants, cholinesterase inhibition, or tetanic stimulation. Because it is noncompetitive this mechanism of action is not affected by increasing the concentration of an agonist such as ACh, nor will the administration of an anticholinesterase improve NM transmission (24).

Extrajunctional Receptors

Normally a very small number of extrajunctional AChRs are incorporated in the muscle plasma membrane. Like junctional receptors, they are glycoproteins; they

have a similar mode of action and under special circumstances can be synthesized by the muscle. Denervation, for example, produces a fivefold to thirtyfold rise in the number of these AChRs per muscle fiber. The number of these receptors begins to increase about 2-3 days after denervation, increases to a peak value usually 1-2 weeks later and then declines slowly (25). Still, the density of these receptors (1600 sites/ μm^2 during peak levels) is estimated to be only 10-15% that of the junctional receptors (26). An unusually large population of extrajunctional receptors can also be found during prolonged immobilization and in embryonic skeletal muscles of several species of animals. Unlike the synaptic receptors, which are firmly fixed to the endplate and are more stable, the extrajunctional receptors are more loosely attached to the cell membrane and can be located over the entire surface of the muscle membrane. Moreover, the turnover rate of extrajunctional receptors is much more rapid, their half-life being on the order of 19-24 hr whereas the half-life of junctional receptors is 1-2 weeks (27,28).

In the normal state, nerve activity serves as the regulatory stimulus inhibiting the biosynthesis of AChRs at extrajunctional sites. In the absence of nerve activity, this inhibition is less in evidence. Months after the denervation of skeletal muscles, for instance, junctional receptors can be detected and extrajunctional receptors still recognized over much of the muscle membrane (7). Similarly, during periods of muscular inactivity the ACh-sensitive zone around the end plates expands to several millimeters and the sensitivity of the muscle to both natural and applied ACh increases (29,30). The formation of extrajunctional receptors can also be induced by postsynaptic mechanisms, such as chronic neuromuscular blockade (3 days) with tubocurarine, succinylcholine (SCh), or α -bungarotoxin, the time course of the appearance of these receptors being rather similar to, and the increase in density of the same magnitude as, that occurring after denervation (31).

In many respects the AChRs in the NM junction and at the extrajunctional sites are indistinguishable. However, some differences do exist, an important one being that tubocurarine binds less readily to the extrajunctional unit (32,33). In consequence, tubocurarine competes less effectively with agonists (ACh) here than at the junctional receptors. Extrajunctional channels opened by agonists remain open for a longer time; moreover, the elementary current is somewhat reduced (34,35). In addition, after denervation relatively insensitive channels that exhibit slower kinetics than the normal sodium junctional channels have been observed to appear near the endplate (36).

Clinically, resistance to nondepolarizing muscle relaxants is found predominantly in the muscles on the affected side of a hemiplegic patient (37-39), or after a severe burn (40,41). Although in these cases direct evaluation of the receptors has not been made, one can presume (based on animal studies) that extrajunctional receptors have developed. Consequently, large doses of nondepolarizing relaxants are required to induce blockade in the paralyzed limbs or the burned patient. Interestingly, some degree of ACh sensitivity is also seen in the unaffected side of such a patient (42). Such sensitivity may be due to generalized reduced activity of the muscles of a hemiplegic patient. A similar situation can be seen in the unrestricted side of an animal one of whose limbs has been casted (43).

Transection of the cord induces a similar situation. A spread of cholinergic receptors from the endplate region is thereafter seen. Should SCh be administered, the denervated muscle will develop contracture, with an increase in serum potassium levels (44). Because these receptors are easily activated by agonists such as SCh, large amounts of potassium can be released during the anesthetic course, resulting in hyperkalemia (45). These receptors are not affected by small doses of nondepolarizers, so prior administration of tubocurarine might attenuate but does not prevent the hyperkalemic response (46).

Development of the Neuromuscular Junction

During development, several changes occur at the myoneural junction (47,48). These have been closely followed in animals (49). In mice, a unique and uniform process involving most of the components of the nerve terminal occurs with aging. In the presynaptic areas, nerve terminal areas as well as mitochondrial and synaptic vesicles decrease, whereas smooth endoplasmic reticulum, coated vesicles, cisternae, and microtubules increase. In the postsynaptic site the junctional folds and subsarcolemmal vesicles become more complex (50).

In animals, each neonatal muscle fiber is innervated by numerous fine processes of several motor axons. This zone is occupied by a high density of AChRs of roughly uniform distribution. During the second postnatal week this polyneuronal innervation of individual muscle fibers is lost. During the third week the distribution of AChRs changes markedly; spots of low AChR density appear that enlarge to form the nonsynaptic regions of the mature junctional zone as the receptors become closely associated with the maturing branches of the motor axon terminals (51). With maturation, the channel gating properties change

from the slowly closing to the rapidly closing type (52). One of the consequences of polyneuronal innervation is that some axons innervate very large numbers of muscle fibers, and these large motor units rapidly decrease in size as the superfluous nerve terminals are eliminated (53-55). This elimination is probably due to withdrawal of the redundant terminals (56). The elimination process is activity-dependent, as evidenced by experiments in which tenotomizing the muscles or treating the nerve with paralyzing drugs (57,58) delays the loss of superfluous nerve terminals. In contrast, increasing the activity of the myoneural junction chemically (58) or by chronic stimulation of the nerves accelerates the process (59). As the motor activity increases with the birth of the animal, the activation of the muscle fibers by ACh will also increase, causing the release of proteolytic enzymes into the synaptic clefts (54). Enzymes will then tend to digest the nerve terminals; the ability of the terminal to survive will depend on the supply of reparative material that it receives from the nerve cell body. As the weaker terminals are withdrawn, the neuron is able to divert more material to its surviving terminal, thus increasing its resistance. Ultimately a nerve terminal will survive when the rate of supply balances the rate of digestion.

Because of the much smaller dimensions of the neonate's NM connections, the number of receptors per NM junction is more than one order of magnitude lower than in mature animal tissue (49,51). Furthermore, embryonic muscle fibers have many more extrajunctional receptors than do innervated adult skeletal muscles; whether they are identical with the extrajunctional receptors found during denervation of adult muscles is a matter of debate (24). Consequently, a moderate level of ACh sensitivity is found in the extrajunctional region of recently innervated frog, rat, and chick skeletal muscles *in vivo* (5). As maturation of the NM system proceeds, this sensitivity is progressively restricted toward the NM junction.

It is important to realize that the distribution of AChRs at the immature NM junction is not especially stable in the absence of the nerve. It is by virtue of the continuing action of the nerve during the postnatal period that the accumulation of AChR molecules at the NM junction occurs (53,59). This trophic action of the neuron on its target cells has recently been confirmed by recording miniature endplate potentials and observing that innervated embryonic muscle cells are maintained in a depolarized state (relative to that of innervated mature muscle cells) by a steady spontaneous release of ACh from the innervating neurite (60). This is a mechanism different from that of quantal ACh release.

It is interesting to note that the turnover rate of AChRs in extrajunctional regions of embryonic diaphragms is rather similar to that of AChR in cultured myotubes and of extrajunctional receptors in denervated adult muscles; all have a rapid turnover rate with a half-life of approximately 24 hr (51). Within a few days (about 6-10), turnover time increases to values characteristic of adult junctional receptors (52).

The AChR cluster is stable once it has formed in the synaptic site of the innervated myotube; any extrajunctional receptor cluster present on a muscle at the time of innervation will disappear. Polyneuronal innervation present on a muscle at the time of innervation will disappear and its decline parallels the loss of extrajunctional receptors. This process begins just before birth in rats and continues for about 3 weeks, at which point an adult junctional receptor distribution has been attained (7).

By the time of birth in rats the receptor accumulation shows a plaquelike morphology. The junctions with this plaquelike morphology are multiply innervated, but the nerve terminals do not appear to cover the entire receptor-dense region of the muscle membrane. With further development all of the receptor-dense postjunctional membrane is found apposed to the nerve terminal (51).

Although some extrajunctional AChRs are found near the NM junction in adult skeletal muscles, the absolute density of these "peri-junctional" receptors is much greater in developing muscles (61). This area seems to be a transitional zone in which the membrane contains receptors with some extrajunctional characteristics and sodium channels with characteristics different from those of the normal membrane (62).

Rates of development vary from one animal to another and from one group of muscles to another (63). An illustrative example is that of the rat extraocular muscles. It has been observed that at the third postnatal day the NM junctions are very small, are not concentrated in the postsynaptic folds and do not contain an abundant number of synaptic vesicles and mitochondria. Within the first week, however, there appears a second type of NM junction with postsynaptic folds and at the second week an extensive number of postsynaptic folds can be found (64).

Human Observations

Though for obvious reasons there are practically no data showing the continuity of human fetal receptor development, some isolated observations have been made. The NM junction is first observed at about the ninth week of gestational age. Primitive motor end-

plates and a few axons are noticed by the twentieth week and a continuous modification of the postsynaptic aggregates occurs between the tenth and twentieth week of human fetal life (65). In children 2 months to 4 yr old, it has been further observed that the postsynaptic area and postsynaptic membrane length are significantly less than in adults (66).

The usual methods for analyzing receptor function (e.g., α -bungarotoxin binding) cannot be used with the intact human being, nor can such instrumentation as single channel recording be employed in moving infants. Certain observations indicating that receptor properties are changing in the developing infant can nonetheless be made with current methodologies.

Mechanical measurements can be made in infants to great effect. During train-of-four stimulation (2 Hz/2 sec) in children, each of the four twitches is practically equal in size (100%). However, in infants less than a month old the fourth evoked response in the train is lower (67). The change to the higher value in the important first month of development indicates probable maturation of the myoneural junction. It is of further interest that premature infants (less than 32 weeks of developmental age) have lower train-of-four values ($83 \pm 2\%$) than most mature neonates (68).

During high frequency stimulation, especially above 1 Hz, the release of ACh mobilizes more ACh to the readily releasable position within the nerve terminals; hence, release keeps pace with the demands of the high frequency stimulation. This effect is presumed to be due to the cholinergic receptors on the prejunctional structures. Blocking these receptors impairs the mobilization of ACh and produces the fade response. By contrast, block of postjunctional receptors diminishes the endplate potential to a point below the threshold at which the muscle will contract. The effect of relaxant at low frequencies of stimulation (0.1 Hz) is therefore thought to be due mostly to the drug's postjunctional action (69,70).

Nondepolarizing muscle relaxants are assumed to produce depression of the fourth twitch of train-of-four (T4) and depression of twitch height by partially independent mechanisms. These mechanisms are not yet well understood, but the effect on T4 seems mostly prejunctional whereas the effect on T1 is postjunctional. During reversal of the NM effects of pancuronium in infants it has been observed that train-of-four ratios are higher at the same level of twitch height (T1) as those measured in older children or adults (71). This datum indicates a less potent prejunctional action of pancuronium in infants or a more potent postsynaptic antagonism by neostigmine.

The frequency sweep electromyogram tests the integrity of muscle by increasing the stimulus frequency

from 1 pulse/sec to a final frequency of 100 Hz over a stimulation period of 10 sec. This exponential increase in frequency allows for NM transmission at tetanic rates but does not induce fatigue. With this technique it has been shown that infants less than 12 weeks of age demonstrate a significantly less pronounced response (more fade) at high stimulation frequencies than do infants older than 12 weeks, in whom the response becomes similar to that in adults (12).

During short tetanic stimulation (5 sec), the fade in infants has been measured at 5% at 20 Hz and 9% at 50 Hz (67). These values are comparable to those of the adult (72). If the duration of stimulation is prolonged, a higher degree of fade may be seen. In small infants, a decrement of more than 50% in the height of tetanus has been observed during 15 sec of tetanic stimulation (11). Not surprisingly, a more marked decrement is seen in premature infants.

Channel Kinetics of Neonatal Receptors

Several kinetic properties of the fetal receptor makes it different from the adult receptor. The single channel currents activated by ACh in spherical "myoballs" from embryonic muscle cells indicate that ACh activates currents of two independent classes each of different amplitude and density, and each apparently arising from separate populations of AChR channels. This indicates that the AChR channels in embryonic muscle adopt, in addition to a 'main' conductance state, a 'substate' of lower conductance (73), the latter representing discrete allosterically activated channels (74). In embryonic rat muscles tubocurarine maintains its clinical action but also behaves as a cholinergic agonist, producing small sustained depolarization that can be blocked by α -bungarotoxin (75). These single channel events are of short duration.

Analysis of the decay time course of miniature endplate current recordings in rats suggests that a conversion of endplate channel gating properties from a slowly relaxing to a rapidly relaxing type (such as that found in the endplate of adult fibers), occurs between 8-18 days of postnatal development (76,36). In newborn animals the nonsynaptic channels have a mean open duration 3-5 times longer than do those of the subsynaptic membrane of the adult (77,78). It is interesting to note that subsynaptic receptors are already metabolically stable at the time of channel conversion. Stabilization of subsynaptic AChRs precedes the conversion of their channel gating properties by at least 1 week, suggesting that receptor and channel properties are controlled by different signals from the nerve terminal. Such a difference indicates that the conversion of synaptic channel gating is due to a mod-

ification of the subsynaptic membrane rather than insertion of a different form of receptor channel complex (76).

In the embryonic myotubes of the rat, tubocurarine activates both a full and a partial state of channel induction. At a low concentration of agonists (ACh vs tubocurarine) the distribution of channel open times is biphasic. A brief channel may result from the binding of a single agonist molecule whereas a longer-lived channel probably results from the binding of two agonist molecules (36,79). In the full open state the channel is probably susceptible to blockade by tubocurarine, whereas in the partial state it is not. The agonist-antagonist effect of tubocurarine can also be observed in the adult muscle, but it is much weaker (80). Furthermore, in the adult the conduction of the channel (activated either by ACh or tubocurarine) is greater than in the myotubes. When the membrane potential is hyperpolarized with higher doses of tubocurarine, the channel blocking effect becomes an important mechanism of blockade (81).

Pharmacologic Observations in Infants

Succinylcholine

Early in 1955 Stead demonstrated that infants, especially neonates, are resistant to the neuromuscular effects of succinylcholine (SCh) (1). A dose of 0.78 mg/kg SCh in infants produced apnea of 50 sec duration whereas in adults a smaller dose of 0.4 mg/kg produced apnea for 2-3 min. Further studies both confirmed the infant's high clinical requirement of SCh and demonstrated that this requirement diminishes with age (82,83). Monitoring of the twitch response provided additional and more refined information. A single intravenous dose of 0.5 mg/kg in children was shown to be equivalent to 1.0 mg/kg in small infants (84) and, during intramuscular administration, 5-6 mg/kg SCh (85) in infants achieved the same degree of neuromuscular block as 4 mg/kg in children (86). The infant's characteristic resistance was also observed during continuous SCh infusion. To maintain an initial twitch depression of more than 90%, significantly more drug was required in infants than in children (87,88). Of special interest was the fact that some infants, ten days to four months, required more than three times the dose that older children required and these infants recovered remarkably rapidly (88). It was also noticed that the development of tachyphylaxis or phase II block was not much different in infants and children. Infants developed phase II block after 5.0 mg/kg SCh and children after 4 mg/kg when the total dose was administered over an interval of 25 min.

One explanation for the greater requirement in infants is their relatively large extracellular volume (39% of body weight vs 20% in adults). Because SCh has a highly ionizable molecule, it distributes itself in a larger pool and the concentration at the myoneural junction is thus less in infants (89,90). However, this pharmacokinetic factor does not explain the remarkable fact that some infants require three to four times the infusion rates of other infants, especially because healthy infants of the same age and weight are assumed to have similar distribution volumes.

Another possibility is based on the fact that the duration of action of SCh is affected by plasma cholinesterase. Infants are known to have low plasma cholinesterase values (about 50% of adult values) (91). If the enzyme level were low enough the action of SCh would be prolonged; however, their levels are not so low as to affect significantly the hydrolysis of SCh. Infants also demonstrate a resistance to the NM effect of decamethonium. This resistance has not been investigated as fully as has the reaction to SCh but it is known that two to three times the dose necessary to produce paresis of the limb muscles in an adult is required for the same response in infants (92).

With our present knowledge it is difficult to explain the infant's marked resistance to succinylcholine, especially during continuous infusion. Larger volumes of distribution might partly explain this phenomenon (89). However, judging from our knowledge of receptors, we might expect a greater sensitivity to SCh because fetal receptors are more sensitive to ACh. Blockade by a depolarizing relaxant depends upon a sharp demarcation between the chemically sensitive receptor channels of the endplate and the chemically insensitive sodium channels in the perijunctional area of the muscle membrane. In contrast to the adult, in whom the boundary is sharp, infants whose junctions are not yet sensitive may have diffuse boundaries in which persistent fetal receptors are in the perijunctional margin (24). In this case, it would be harder to establish a blockade of neuromuscular transmission with a depolarizing agent.

Nondepolarizing Muscle Relaxants

In Stead's study, two infants were noted to be markedly sensitive to the neuromuscular effects of tubocurarine (1). Several subsequent studies demonstrated that infants require less tubocurarine than adults or older children for adequate control of ventilation and satisfactory operating conditions (2,93).

When electromyographic studies of the effect of nondepolarizing relaxants on peripheral muscles are evaluated in neonates, no particular sensitivity to tu-

bocurarine is found in the hand muscle of the neonate relative to adults (94). However, clinically the respiratory tidal volume of the neonate diminishes *pari passu* with paresis of the hand muscles, whereas in adults paresis of hand muscles can occur without any significant change in tidal volume.

When the force of contraction of the thumb (twitch response) is measured no significant difference is found between infants and children in the mean dose-response curves for nondepolarizing muscle relaxants. However, there is marked variation in responses of the neonate, some being very resistant to tubocurarine and others quite sensitive (95).

Several pharmacokinetic factors also differentiate the neonate from the adult. The free fractions of tubocurarine and metocurine, for example, are greater in the blood of newborns than in maternal blood (96). Consequently, at the same plasma level (if the measured parameter is the total amount) neonatal blood has a greater fraction of free relaxant available to act at the myoneural junction. Pharmacokinetic studies have also shown that the neonate requires a lower total plasma tubocurarine level than children or adults to produce similar effects. The plasma tubocurarine concentration at which 50% depression of the electromyogram occurs was observed to be lower in the neonate than in the older infant and significantly lower in both than in children or adults. The steady state distribution volume ($V_{d_{ss}}$) is less in infants than in neonates, less again in children, and least in adults. The product of the two (D_{50}) is comparable in all groups (97). These data indicate that as a group neonates require a lower plasma tubocurarine concentration than children or adults to achieve the same degree of relaxation. Because this effect is partially counteracted in small infants by their larger extracellular volume, they tend to require about the same clinical amount of the drug. The same tendency has been observed with atracurium and vecuronium (98,99), although not as clearly as with tubocurarine.

In a more recent trial the plasma concentration of tubocurarine required to produce the same degree of neuromuscular paralysis was found to be no different in adults, infants, and most neonates. However, two neonates (out of seven) showed marked resistance to the neuromuscular blocking effect of tubocurarine, requiring about three times the concentration of the average child (100). This difference cannot be explained by pharmacokinetic data; hence one can assume the reason to stem from characteristics unique to the NM junction, receptor, or nerve ending of the newborn.

Limitations inherent in our methodologies prohibit us from concluding with certainty regarding the cause

of the different response of the neonatal NM junction to muscle relaxants. α -Bungaratoxin cannot be used in humans. The patch clamping technique is employed with only moderate success, as it does not always record electrical activity—the absence of electric activity might not imply the absence of receptors, but rather an incomplete or faulty contact with the receptors. In any case, no data on patch clamping in humans presently exist. Extrapolating from the animal model we can hypothesize that infants who are sensitive to tubocurarine probably retain fetal channels with prolonged intervals that remain open for a longer time in the presence of the relaxant. Infants who are extremely resistant to tubocurarine probably are born with a large number of fetal receptors. Fetal receptors, we know (at least in animals) are quite similar to extrajunctional receptors and hence may be resistant to binding with tubocurarine (5). We do know that the human neonate may occasionally require larger amounts of tubocurarine. Because this is true only in the first few weeks of life, we can presume that healthy infants promptly rid themselves of fetal receptors.

From the presently available data we can conclude that some developmental changes occur in the human NM junction for at least several months after birth. The specific stages cannot be pinpointed nor clinically predicted; we can deduce only that they occur in different infants at different rates. We expect that with further investigations of the NM function, new information will be obtained to provide better answers.

The authors are indebted to Mr. Michael Gionfriddo for reviewing and editing the manuscript, and to Ms. Kitt Booher for her help in assembling the pertinent material.

References

1. Stead AL. The response of the newborn infant to muscle relaxants. *Br J Anaesth* 1955;27:124-30.
2. Bush GH, Stead AL. The use of *d*-tubocurarine in neonatal anaesthesia. *Br J Anaesth* 1962;34:721-8.
3. Curless RG. Developmental patterns of peripheral nerve, myoneural junction and muscle: a review. *Prog Neurobiol* 1977;9:197-209.
4. Kelly SS, Roberts DV. The effect of age on the safety factor in neuromuscular transmission in the isolated diaphragm of the rat. *Br J Anaesth* 1977;49:217-21.
5. Fambrough DM. Control of acetylcholine receptors in skeletal muscles. *Physiol Rev* 1979;59:165-227.
6. Peper K, Bradley RJ, Dreyer F. The acetylcholine receptor at the neuromuscular junction. *Physiol Rev* 1982;62:1271-340.
7. Bennett MR. Development of neuromuscular synapses. *Physiol Rev* 1983;63:915-1045.
8. Adams DJ, Bevan S. Some properties of acetylcholine receptors in human cultured myotubes. *Proc Roy Soc Lond* 1985;224:183-96.

9. Goudsouzian NG. The Physiology and pharmacology of neuromuscular transmission in infants and children. In: Steward DJ, ed. Some aspects of Paediatric Anaesthesia. Monographs in Anaesthesia. Amsterdam: Excerpta Medica, 1981:59-77.
10. Goudsouzian NG. Muscle relaxants in infants and children. *Can Anaesth Soc J* 1985;32:527-31.
11. Koenigsberger MR, Patten B, Lovelace RE. Studies of neuromuscular function in the newborn: a comparison of myoneural function in the full term and the premature infant. *Neuropadiatrie* 1973;4:350-61.
12. Crumrine RS, Yodowski EY. Assessment of neuromuscular function in infants. *Anesthesiology* 1981;54:29-32.
13. Popot J-L, Changeux J-P. Nicotinic receptor of acetylcholine: Structure of an oligomeric integral membrane protein. *Phys Rev* 1984;64:1162-239.
14. Stroud RM. Acetylcholine receptor structure. *Neuroscience Commentaries* 1983;1:124-38.
15. Karlin A. The anatomy of a receptor. *Neuroscience Commentaries* 1983;1:111-23.
16. Claudio T, Ballivet M, Patrick J, Heinemann S. Nucleotide and deduced amino acid sequences of Torpedo californica acetylcholine receptor gamma subunit. *Proc Nat Acad Sci (USA)* 1983;80:1111-5.
17. Lee CY. Chemistry and pharmacology of polypeptide toxins in snake venoms. *Ann Rev Pharmacol* 1972;12:265-86.
18. Dreyer F. Acetylcholine receptor. *Br J Anaesth* 1982;54:115-30.
19. Hirokawa N, Heuser JE. Internal and external differentiations of the postsynaptic membrane at the neuromuscular junction. *J Neurocyt* 1982;487-510.
20. Daniels MP, Vogel Z. Immunoperoxidase stressing of α -bungarotoxin binding sites in muscle end-plates shows distribution of acetylcholine receptors. *Nature (London)* 1975;254:339.
21. Fertuck HC, Salpeter MM. Quantitation of junctional and extrajunctional acetylcholine receptors by electron microscope autoradiography after 1α -bungarotoxin binding at mouse neuromuscular junction. *J Cell Biol* 1976;69:144-58.
22. Adams PR. Acetylcholine receptor kinetics. *J Membrane Biol* 1981;58:161-74.
23. Standaert FG. Donuts and Holes. Molecules and muscle relaxants. *Seminars in Anesthesia* 1984;III(4):251-61.
24. Standaert FG. Basic physiology and pharmacology of the neuromuscular junction. In: Miller RD, ed. *Anesthesia*. New York: Churchill-Livingston 1986:835-71.
25. Almon RR, Appel SH. Cholinergic sites in skeletal muscles. I Denervation effects. *Biochemistry* 1976;15:3662-7.
26. Hartzell HG, Fambrough DM. Acetylcholine receptors. Distribution and extrajunctional density in rat diaphragm after denervation correlated with acetylcholine sensitivity. *J Gen Phys* 1972;60:248-62.
27. Devreotes PN, Fambrough DM. Acetylcholine receptor turnover in membranes of developing muscle fibres. *J Cell Biol* 1975;65:335-58.
28. Chang CC, Huang MC. Turnover of junctional and extrajunctional acetylcholine receptors of rat diaphragm. *Nature* 1975;253:643-4.
29. Fambrough DM, Devreotes PN, Card DJ. The synthesis and degradation of acetylcholine receptors. In: Cottrell GA, ed. *Synapses*. Glasgow: PNR Usherwood, 1977:202-36.
30. Fischbach GD, Robbins A. Effect of chronic disuse on rat soleus neuromuscular junctions on postsynaptic membrane. *J Neurophysiol* 1971;34:562-9.
31. Berg DK, Hall ZW. Increased extrajunctional acetylcholine sensitivity produced by chronic postsynaptic neuromuscular blockade. *J Physiol (London)* 1975;244:659-76.
32. Beranek R, Vyskocil F. The action of tubocurarine and atropine in the normal and denervated rat diaphragm. *J Physiol (London)* 1967;188:53-66.
33. Chiu THAJ, Lapa EA, Barnard EA, Albuquerque EX. Binding of d -tubocurarine and α -Bungarotoxin in normal and denervated mouse muscles. *Exp Neurol* 1974;43:399-413.
34. Neher E, Sakmann B. Single channel currents recorded from membrane of denervated frog muscle fibres. *Nature (London)* 1976;260:799-802.
35. Brenner HR, Sakmann B. Neurotrophic control of channel properties at neuromuscular synapse of rat muscles. *J Physiol (London)* 1983;337:159-71.
36. Pappone PA. Voltage-clamp experiments in normal and denervated mammalian skeletal muscle fibres. *J Physiol* 1980;306:377-410.
37. Graham DH. Monitoring neuromuscular block may be unreliable in patients with upper-motor-neuron lesions. *Anesthesiology* 1980;52:74-5.
38. Moorthy SS, Hilgenberg JC. Resistance to non-depolarizing muscle relaxants in paretic upper extremities of patients with residual hemiplegia. *Anesth Analg* 1980;59:624-7.
39. Iwasaki H, Namiki A, Omote K, Omote T, Takahashi T. Response differences of paretic and healthy extremities to pancuronium and neostigmine in hemiplegic patients. *Anesth Analg* 1985;64:864-6.
40. Martyn JAJ, Szyfelbein SK, Ali HH, Matteo RS, Savarese JJ. Increased d -tubocurarine requirement following major thermal injury. *Anesthesiology* 1980;52:352-5.
41. Martyn JAJ, Goudsouzian NG, Matteo RS, Liu LMP, Szyfelbein SK, Kaplan RF. Metocurine requirements and plasma concentrations in burned pediatric patients. *Br J Anaesth* 1983;55:263-8.
42. Shayevitz JR, Matteo RS. Decreased sensitivity to metocurine in patients with upper motor neuron disease. *Anesth Analg* 1985;64:767-72.
43. Waud BE, Amaki Y, Waud DR. Disuse and d -tubocurarine sensitivity in isolated muscles. *Anesth Analg* 1985;64:1178-82.
44. Carter JC, Sokoll MD, Gergis SD. Effect of spinal cord transection on neuromuscular function in the rat. *Anesthesiology* 1981;55:542-6.
45. Gronert GA. Disuse atrophy with resistance to pancuronium. *Anesthesiology* 1981;55:547-9.
46. Azar I. The response of patients with neuromuscular disorders to muscle relaxants: a review. *Anesthesiology* 1984; 61:173-87.
47. Redfern PA. Neuromuscular transmission in newborn rats. *J Physiol* 1970;209:701-9.
48. Fambrough DM, Hartzell HC. Acetylcholine receptors: number and distribution at neuromuscular junctions in rat diaphragm. *Science* 1972;176:189-91.
49. Grinnel AD, Herrera AA. Specificity and plasticity of neuromuscular connections. Long term regulation of neuron function. *Progr Neurobiol* 1981;17:203-82.
50. Fahim MA, Robbins N. Ultrastructural studies of young and old mouse neuromuscular junctions. *J Neurocytol* 1982; 11:641-56.
51. Steinbach JH. Developmental changes in acetylcholine receptor aggregates at rat skeletal neuromuscular junctions. *Develop Biol* 1981;84:267-76.
52. Michler A, Sakmann B. Receptor stability and channel con-

- version in the subsynaptic membrane of the developing mammalian neuromuscular junction. *Developmental Biol* 1980;80:1-17.
53. Brown MC, Jansen JKS, Van Essen D. Polyneuronal innervation of skeletal muscles in newborn rats and its elimination during maturation. *J Physiol* 1976;261:387-422.
54. O'Brien RAD, Ostberg AJC, Vrbova G. The reorganization of neuromuscular junctions during development in rats. *Membranes in growth and development*. New York: Alan R. Liss, 1982:247-57.
55. Taxt T, Ding R, Jansen JKS. A note on the elimination of polyneuronal innervation of skeletal muscles in neonatal rats. *Acta Physiol Scand* 1983;117:557-60.
56. Riley DA. Ultrastructural evidence for axon retraction during spontaneous elimination of polyneuronal innervation of rat soleus muscle. *J Neurocytol* 1981;10:425-40.
57. Riley DA. Tenotomy delays the postnatal development of the motor innervation of the rat muscles. *Brain Res* 1978;143:162-7.
58. Duxson M. The effect of postsynaptic block in development of the neuromuscular junction in postnatal rats. *J Neurocytol* 1982;11:395-408.
59. Duxson MJ, Vrbova G. Inhibition of acetylcholinesterase accelerates axon terminal withdrawal at the developing rat neuromuscular junction. *J Neurocytol* 1985;14:337-63.
60. Sun Yi-An, Poo Mu-Ming. Non-quantal release of acetylcholine at developing neuromuscular synapses in children. *J Neuroscience* 1985;5:634-42.
61. Bevan S, Steinbach JH. The distribution of α -bungarotoxin binding site in mammalian skeletal muscles developing in vivo. *J Physiol* 1977;267:195-213.
62. Betz WJ, Caldwell JH, Kinnaman SC. Increased sodium conductance in the synaptic region of rat skeletal muscle fibres. *J Physiol (London)* 1984;352:189-202.
63. Hopkins NG, Brown MC, Keynes RJ. Postnatal growth of motor nerve terminals in the muscles of the mouse. *J Neurocytol* 1985;14:525-40.
64. Nag AC, Cheng M. Differentiation of fibre types in an extraocular muscle of the rat. *J Embryol Exp Morph* 1982;71:171-91.
65. Fidzianska A. Human ontogenesis. II. Development of the human neuromuscular junction. *J Neuropathol Exp Neurol* 1980;39:606-15.
66. Arizono N, Koreto O, Iwai Y, Hidaka T, Takeoka O. Morphometric analysis of human neuromuscular junction in different ages. *Acta Path Jpn* 1984;34:1243-9.
67. Goudsouzian NG. Maturation of neuromuscular transmission in the infant. *Brit J Anaesth* 1980;52:205-14.
68. Goudsouzian NG, Crone RK, Todres ID. Recovery from pancuronium blockade in the neonatal intensive care unit. *Br J Anaesth* 1981;53:1303-9.
69. Bowman WC. Prejunctional and postjunctional cholinceptors at the neuromuscular junction. *Anesth Analg* 1980;59:935-43.
70. Meakin G, Sweet PT, Bevan JC, Bevan DR. Neostigmine and edrophonium as antagonists of pancuronium in infants and children. *Anesthesiology* 1983;59:316-21.
71. Bowman WG, Gibb AJ, Marshall IG. Prejunctional and postjunctional effects of vecuronium. In: Agoston S, Bowman W, Miller R, Viby-Morgenson J, eds. *Clinical experiences with Norcuron*. Amsterdam: Excerpta Medica, 1983:26-32.
72. Stanec A, Heyduk J, Stanec G, Orkin L. Tetanic fade and posttetanic tension in the absence of neuromuscular blocking agents in anesthetized man. *Anesth Analg* 1978;57:102-7.
73. Hamill OP, Sakmann B. Multiple conductance states of single acetylcholine receptor channels in embryonic muscle cells. *Nature* 1981;294:462-4.
74. Morris CE, Montpetit M. Multiple conductance states of the acetylcholine receptor channel complex. *Can J Physiol Pharmacol* 1985;64:347-355.
75. Morris CE, Wong BS, Jackson MB, Lecar H. Single-channel currents activated by curare in cultured embryonic rat muscles. *J Neuroscience* 1983;3:252-3.
76. Michler A, Sakmann B. Receptor stability and channel conversion in the subsynaptic membrane of the developing mammalian neuromuscular junction. *Develop Biol* 1980;80:1-17.
77. Fischbach GD, Schuetze SM. A postnatal decrease in acetylcholine channel open time at rat end-plate. *J Physiol (London)* 1980;303:125-37.
78. Kullberg R, Kaspazay H. Gating kinetics of nonjunctional acetylcholine receptor channels in the developing xenopus muscle. *J Neuroscience* 1985;5:970-6.
79. Takeda K, Trautmann A. A patch clamp study of the partial agonist actions of tubocurarine on rat myotubes. *J Physiol (London)* 1984;349:353-74.
80. Trautmann A. Curare can open and block ionic channels associated with cholinergic receptors. *Nature (London)* 1982;298:272-5.
81. Trautmann A. Tubocurarine, a partial agonist for cholinergic receptors. *J Neural Transmission Suppl* 1983;18:353-61.
82. Telford J, Keats AS. Succinylcholine in cardiovascular surgery of infants and children. *Anesthesiology* 1957;18:841-8.
83. Nightingale DA, Glass AG, Backmann L. Neuromuscular blockade of succinylcholine in children. *Anesthesiology* 1966;27:736-41.
84. Cook DR, Fischer CG. Neuromuscular blocking effects of succinylcholine in infants and children. *Anesthesiology* 1975;42:662-5.
85. Liu LMP, Goudsouzian NG. Neuromuscular effects of intramuscular succinylcholine in infants. *Anesthesiology* 1982;57:A413.
86. Liu LMP, DeCook T, Goudsouzian NG, Ryan JF, Liu P. Dose response to intramuscular succinylcholine in children. *Anesthesiology* 1981;55:599-602.
87. DeCook TH, Goudsouzian NG. Tachyphylaxis and phase II block development during infusion of succinylcholine in children. *Anesth Analg* 1980;59:639-43.
88. Goudsouzian NG, Liu LMP. The neuromuscular response of infants to a continuous infusion of succinylcholine. *Anesthesiology* 1984;60:97-101.
89. Zsigmond EK, Downs JR. Plasma cholinesterase activity in newborns and infants. *Can Anaesth Soc J* 1971;18:278-85.
90. Cook DR. Muscle relaxants in infants and children. *Anesth Analg* 1981;60:335-43.
91. Cook DR, Fischer CG. Characteristics of succinylcholine neuromuscular blockade in neonates. *Anesth Analg* 1978;57:63-8.
92. Churchill-Davidson HG, Wise RP. Neuromuscular transmission in the newborn infant. *Anesthesiology* 1963;24:271-8.
93. Walts LF, Dillon JB. The response of newborns to succinylcholine and *d*-tubocurarine. *Anesthesiology* 1969;31:35-8.
94. Churchill-Davidson HC, Wise RP. The response of the newborn infant to muscle relaxants. *Can Anaesth Soc J* 1964;11:1-6.
95. Goudsouzian NG, Donlon JV, Savarese JJ, Ryan JF. Reevaluation of *d*-tubocurarine dosage and duration in the pediatric age groups. *Anesthesiology* 1975;43:416-25.
96. Wood MB, Wood AJJ. Changes in plasma drug binding and

- α_1 -acid glycoprotein in mother and newborn infant. Clin Pharmacol Ther 1981;28:522-6.
97. Fisher DM, O'Keeffe C, Stanski DR, Cronnelly R, Miller RD, Gregory G. Pharmacokinetics and dynamics of *d*-tubocurarine in infants, children and adults. Anesthesiology 1982;57:203-8.
98. Brandom BW, Stiller RL, Cook DR, Woelfel SK, Charkzavorti S, Lai A. Pharmacokinetics of atracurium in anesthetized infants and children. Clin Pharmacol Ther 1986 (in press).
99. Fisher DM, Castanoli K, Miller RD. Vecuronium kinetics and dynamics in anesthetized infants and children. Clin Pharmacol Ther 1985;37:402-6.
100. Matteo RS, Lieberman IG, Salanitro E, McDaniel DD, Diaz J. Distribution, elimination and action of *d*-tubocurarine in neonates, infants, children, and adults. Anesth Analg 1984;63:799-804.

Clinical Reports

Assessment of Sterility of Pulmonary Arterial Catheter Sheaths

Michael J. Murray, MD, PhD, Mark Wignes, RRT, and John C. McMichan, MBBS, PhD

Since its description in 1970, the flow-directed balloon-tipped pulmonary arterial catheter (PAC) has become a cornerstone for hemodynamic monitoring in the intensive care unit. As the PAC is used more frequently, a subset of patients arises in which, after an initial monitoring success, the catheter fails to wedge. The best way to reposition the catheter in this circumstance is the subject of debate (1). Some physicians think that the catheter should not be advanced after the initial placement because of the possibility of introducing into the patient a part of the catheter that is no longer sterile (2).

In an attempt to safely manipulate the PAC after placement, Kopman and Sandza (3) developed a plastic sleeve that was put over the catheter at the time of insertion. In 10 patients the sleeve was reported to preserve the sterility of that portion of the catheter that remained outside the patient but within the sheath. Several manufacturers now produce such "contamination sheaths" that are promoted as a means of maintaining the sterility of the catheter and decreasing the infection rates of these catheters.

In their initial study, Kopman and Sandza failed to report whether any of the catheters were manipulated within the sheath prior to the cultures being obtained. Furthermore, swabbing the PAC, as they did, may not be the most effective way to assess the sterility of the catheter. Finally, the number of catheters studied may have been too small to adequately detect contamination.

The purpose of this study then was to assess, by two different techniques, whether a currently marketed contamination sheath does indeed safeguard the sterility of the part of the PAC that lies outside the patient.

Methods

After approval of the project by the Institutional Review Board, 50 patients were enrolled in the study. Only noninfected patients undergoing major vascular surgery were included. Patients in whom the PAC was manipulated within the sheath after insertion and before termination of invasive monitoring were excluded.

After skin preparation with povidone-iodine and draping with sterile towels, the PAC, with the contamination sheath (Cordis Corporation, Miami, FL) attached, was placed through an introducer in the internal jugular vein. Procedures were performed prior to surgery by physicians wearing caps, masks, sterile gloves, and gowns (4).

The duration of pulmonary arterial catheterization was recorded for each patient. At the time that hemodynamic monitoring was discontinued, the distal contamination sheath was swabbed with isopropyl alcohol, and 10 ml of nonbactericidal 5% dextrose in lactated Ringer's solution was injected into the sheath, agitated throughout the length of the sheath, and withdrawn utilizing a sterile technique.

Using sterile scissors, the sheath was then cut in two to expose 5 cm of the PAC immediately outside the introducer. The PAC was then cross-clamped distally (the pressure trace was monitored to assure adequacy of occlusion) to prevent subsequent air embolism. With the cross-clamp in place, a second sterile scissors was used to sever a 5-cm segment of the PAC that was dropped into a sterile test tube. In the laboratory it was rolled across a chocolate blood agar plate (CBAP) utilizing Maki's semi-quantitative technique (5). The catheter segment was then dropped into a test tube containing enriched brain heart infusion broth (EBHIB). The solution collected from the sheath was inoculated on CBAP with a 0.01-ml loop for quantitative assessment. An additional 0.1 ml aliquot was inoculated in EBHIB. All media were incubated at 35°C in 5–10% CO₂ for 7 days. Cultures

Received from the Division of Critical Care, Mayo Clinic and Mayo Foundation, Rochester, MN 55905. Accepted for publication June 2, 1986.

Address correspondence to Dr. Murray, Mayo Clinic, 200 First Street SW, Rochester, MN 55905.

Table 1. Characteristics of Patients with Positive Cultures

Surgical procedure	Duration of catheterization (hr)	Technique	Organism
Femoro-femoral bypass	106	A	<15 CFU, <i>Serratia marcescens</i>
Endarterectomy, left renal artery	24	B	SCN
Right lower lobectomy	20	B	SV
Aorto-femoral bypass	72	A	<15 CFU, SCN
Left renal artery bypass	47	C	>15 CFU, SV
			<15 CFU, <i>Neisseria</i>
Aorto-iliac bypass	27	A	>15 CFU, SV
Aorto-femoral bypass	23	A	>15 CFU, SV
Abdominal aortic aneurysmectomy	120	B	SCN
Abdominal aortic aneurysmectomy	42	B	SCN
Aorto-femoral bypass	22	A	<15 CFU, SCN
Abdominal aortic aneurysmectomy	49	B	SCN

Abbreviations: A, Semiquantitative of PAC segment; B, fluid wash of interior of sheath; C, PAC segment in broth; SCN; *Staphylococcus*, coagulase negative; SV, *Streptococcus viridans*; CFU, Colony forming units.

were examined daily. The catheter segment or fluid was culture positive if either the EBHIB or the CBAP had evidence of bacterial or fungal growth. When the CBAPs were positive, the number of colony forming units (CFU) was reported.

All PAC tips were cultured at the time of removal as part of routine infection surveillance. At the time of removal, after the study procedure had been performed, 5 cm of the tip of the catheter was sent for bacteriologic study.

Seventy-two hours after the catheter was removed, the chart and laboratory data were reviewed. We rechecked the medical record to make sure that no catheters had been manipulated while in the sheath and to document that no patient was infected or had evidence of infection. Furthermore, we sought evidence for any infection that coincided with the time the PAC was in place. All reports (blood, urine, and sputum) for those patients who, because of their clinical findings, had had cultures ordered were obtained. Finally, the culture reports on all the PAC tips were reviewed.

Results

Of the 50 patients enrolled in the study, three were excluded because, in retrospect, they had evidence of infection on admission into the study. Six more patients were excluded because the PAC had been manipulated within the sheath prior to removal. Forty-one patients then had culture results suitable for analysis.

Six (15%) of the patients had catheter segments that were positive for bacterial growth (Table 1). Of these only one was positive in EBHIB. Of the five positive by the semiquantitative technique, three had less than

and two greater than 15 CFU/ml. An additional five patients (12%) had the fluid wash of the sheath positive for bacterial growth (Table 1). All five were positive in EBHIB only.

Of the 41 patients then, 11 had evidence of bacterial contamination, for a total of 26.8% (95% confidence limits 14.2–42.9%). In no patients were both the sheath fluid and the catheter segment positive by culture. None of the 11 patients with bacterial contamination had a positive culture of the tip of the PAC. None had evidence of septicemia, nor was there documentation of any systemic infection. No cultures from patients (blood, wound, or urine) were positive for the same organism as that found growing on the PAC segment or within the contamination sheath. It should be noted that of the 41 patients in the study, none had a positive culture of the tip of the PAC.

There was no apparent relationship between the duration of catheterization and the number of positive cultures. Four of 14 (29%) of cultures taken on catheters removed within 24 hr had growth. Likewise, the number of contaminated PACs was $\frac{3}{15}$ (20%) in the 24–48-hr interval, $\frac{2}{6}$ (33%) in the 48–72 hr interval, and $\frac{2}{6}$ (33%) for PACs left in greater than 72 hr.

Discussion

There are several risks associated with pulmonary artery catheterization (6–9), including the possibility of localized or systemic infection (10–13). To decrease the risk of infection associated with this technique, as well as to facilitate manipulation of a PAC that is not functioning properly, a sheath or shield to cover the external portion of the PAC was described in 1978 by two groups of investigators (3,14).

Kopman and Sandza discussed such a sheath, and

Table 2. Summary of Current Literature

Investigator	Number of patients	Number of patients with positive cultures (%)	Technique
Kopman and Sandza (3)	10	0 (0)	Swab of sheath
Gomez et al. (15)	20	0 (0)	Not described
Groeger et al. (17)	38	7 (18)	Swab of sheath
Baele et al. (18)	73	9 (12)	Swab of valve of the sheath connector
Heard et al. (16)	59	8 (14)	Semiquantitative of PAC segment
Murray et al.	41	6 (15)	Semiquantitative of PAC segment
		5 (12)	Fluid wash of sheath interior

reported that in 10 patients with the PAC so protected, the sterility of the catheter was preserved (3). In the same year, Gomez et al. described a similar shield; no organisms were cultured from consecutive specimens taken from 20 pulmonary arterial catheters at the time of removal from 20 patients (14). However, although the sheath was similar in the latter study, there was an important difference: the sheath was irrigated with 6 ml of a bactericidal solution after placement.

In our present study, using two different techniques, we have found that 27% of the sheaths or catheter segments within the sheath had evidence for colonization. None of the catheter tips from these same patients grew the same organism, nor were any blood or urine cultures so positive. Kopman and Sandza studied a much smaller group of patients, which might explain their negative results (3). Gomez et al. irrigated their sheaths with bactericidal agents, which may explain their zero incidence of positive cultures, but they did not describe how their cultures were obtained (14).

A review of the literature published since 1978 (Table 2) reveals that several other investigators have isolated organisms approximately 15–20% of the time growing on the interior of the sheath (15), on the externalized portion of the PAC within the sheath (16), or from the connector of the sheath to the introducer (17). In one of these studies, $\frac{1}{10}$ patients with a positive sheath culture had the same organism identified in their blood (15). In another report Groeger et al. found a significantly increased incidence of positive cultures (PACs, introducers, sheaths) in patients whose catheters had a contamination shield compared to those whose did not (16). Davies et al., using a similar type of sheath, did not routinely culture the catheters or the sheaths, but did have a 2% incidence of septicemia of their 220 patients (18). In this latter study there were two different kinds of contamination sheaths used, with different techniques employed to maintain sterility, which makes interpretation diffi-

cult. The important point is that even with a sheath there was a 2% incidence of bacteremia.

As to why the sheaths did not maintain the sterility of the PAC, there are several possibilities to be considered. The catheter may have become contaminated during insertion, or, more likely, because the hub of the sheath does not form an airtight fit where it adjoins the PAC introducer, organisms may simply have migrated in. In the one study in which the connector was specifically cultured, nine of 74 (12%) were positive for organisms (17).

Insertion of a bactericidal solution into the sheath when the sheath is placed over the PAC may maintain the sterility of the PAC (14), but our study was not designed to address that issue.

The significance of our findings is a matter of debate. Two different techniques were necessary to observe the incidence of contamination in our study. Using Maki's semiquantitative technique, only two of 41 PAC segments had >15 colony forming units, meeting the criterion for colonization. Furthermore, the organisms we cultured were not particularly virulent. None of our patients showed evidence of bacteremia, nor were PAC tips positive for organisms. This was a special group of patients. They had no other major medical illnesses except for their vascular disease, they were not infected at entry into the study, and did not have the PACS manipulated within the sheath. In this select group, the sheaths did not do what they were designed to do, that is, maintain the sterility of the catheter that remained within the sheath.

These results then call into question the routine use of such contamination sheaths as a means to protect the sterility of the external portions of PACs. One might argue that without the sheaths all of the catheter lying outside the patient is contaminated; the sheath then lowers the positive culture rate from 100 to 27%. The sheaths though may afford a false sense of security: routine nursing care of the insertion site may become lax, and the catheter may be advanced or manipulated despite the fact that it is not truly

sterile. Finally, if the PAC segment within the sheath is not sterile, and yet there is no increased incidence of positive PAC-tip cultures, then the sheaths and their attendant costs are unnecessary and may indeed be detrimental for the reasons discussed.

In summary, a currently marketed contamination sheath failed to maintain the sterility of 11 of 41 pulmonary arterial catheters to which it was applied. No adverse outcomes were noted in these patients, but a larger series of patients may be required to detect such a difference. Other techniques to maintain the sterility of the catheter, e.g., irrigating the sheath with povidone-iodine at placement, may be required.

We acknowledge with gratitude the assistance of Mrs. Julie Schwartz in preparation of this manuscript.

References

1. Applefeld JJ, Caruthers TE, Reno DJ, Civetta JM. Assessment of the sterility of long-term cardiac catheterization using the thermodilution Swan-Ganz catheter. *Chest* 1978;74:377-80.
2. Shaffer LJ. Sterility and repositioning of the Swan-Ganz catheter (editorial). *Chest* 1979;75:743.
3. Kopman EA, Sandza JG Jr. Manipulation of the pulmonary-artery catheter after placement. Maintenance of sterility. *Anesthesiology* 1978;48:373-4.
4. McMichan JC, Michel L. Guide wire-sheath technique for pulmonary artery catheterization and central vein cannulation. *Intensive Care Med* 1979;5:37-9.
5. Maki DG, Weise CE, Sarafin NW. A semiquantitative culture method for identifying intravenous catheter related infection. *N Engl J Med* 1977;296:1305-7.
6. Foote GA, Schabel SI, Hodges M. Pulmonary complications of the flow-directed balloon-tipped catheter. *N Engl J Med* 1974;290:927-31.
7. Sprung CL, Jacobs LJ, Caralis PV, Karpf M. Ventricular arrhythmias during Swan-Ganz catheterization of the critically ill. *Chest* 1981;79:413-5.
8. Sprung CL, Pozen RG, Rozanski JJ, Pinero JR, Eisler BR, Castellanos A. Advanced ventricular arrhythmias during bedside pulmonary artery catheterization. *Am J Med* 1982;72:203-8.
9. Shah KB, Rao TLK, Laughlin S, El-Etr AA. A review of pulmonary artery catheterization in 6245 patients. *Anesthesiology* 1984;61:271-5.
10. Elliott CG, Zimmerman GA, Clemmer TP. Complications of pulmonary artery catheterization in the care of critically ill patients. A prospective study. *Chest* 1979;76:647-52.
11. Singh S, Nelson N, Acosta I, Check FE, Puri VK. Catheter colonization and bacteremia with pulmonary and arterial catheters. *Crit Care Med* 1982;10:736-9.
12. Boyd KD, Thomas SJ, Gold J, Boyd AD. A prospective study of complications of pulmonary artery catheterizations in 500 consecutive patients. *Chest* 1983;84:245-9.
13. Michel L, Marsh M, McMichan J, Southorn P, Braver NS. Infection of pulmonary artery catheters in critically ill patients. *JAMA* 1981;245:1032-6.
14. Gomez F, Spagna P, Lemole GM. Improved techniques in using the Swan-Ganz catheter. *Ann Thorac Surg* 1979;27:468-71.
15. Heard SO, Davis RF, Shereertz RJ, Gallagher RC, Layon AJ, Gallagher TJ. Efficacy of sterile protective sleeves in maintaining sterility of pulmonary artery catheters after insertion. Boston, MA: Society of Cardiovascular Anesthesiologists 5th Annual Meeting, 1984.
16. Groeger J, Carlon GC, Howland WS. Contamination shields for pulmonary artery catheters. *Crit Care Med* 1983;2:230.
17. Baele P, Pedemonte O, Zech F, Kestens-Servaye Y. Clinical use and bacteriological studies of catheter contamination sleeves. *Intensive Care Med* 1984;10:297-300.
18. Davies MJ, Cronin KD, Domaingue CM. Pulmonary artery catheterization. An assessment of risks and benefits in 220 surgical patients. *Anaesth Intensive Care* 1982;10:9-14.

Difficulty Reversing Drug-induced Coma in a Patient with Sleep Apnea

Stanley I. Samuels, MD, and Wendy Rabinov, MD

The syndrome of sleep apnea is of interest to anesthesiologists because these patients frequently present problems of airway management. Moreover, patients with this condition may have a markedly increased response to sedative drugs (1). We report the case of a previously healthy patient in whom sedative drugs produced both respiratory depression and a comatose state that naloxone and physostigmine failed to reverse. We believe that this is the first reported case of drug antagonists that are effective in normal individuals proving ineffective in patients with sleep apnea.

Case Report

A 38-yr-old white male was admitted to the emergency room with an open fracture of the distal right tibia which he sustained at work. Physical examination revealed an alert, oriented male, 210 cm tall, weighing 100 kg with normal vital signs. The patient was noted to have a large neck and a small mouth. Examination of the cardiovascular, respiratory, and neurologic systems revealed no abnormalities. He took no medications and had no allergies. His last meal had been 3 hr before the accident. He had no alcohol intake. He had no prior anesthesia history. In the emergency room the patient was given meperidine 50 mg and promethazine 25 mg for both pain relief and preoperative medication. These drugs were administered by deep intramuscular injection. The drug doses were recorded on the emergency room sheet and were subsequently verified by toxicology screening (discussed below). After discussion with the patient and surgeons, reduction of the fracture under spinal anesthesia was planned.

One hour after preoperative medication, the patient was brought to the operating room and spinal anesthesia was initiated with tetracaine hydrochloride 10 mg and dextrose 10 mg. During the lumbar tap, which was carried out in the right lateral decubitus position, it was noted that the patient was soundly asleep and snoring loudly. There were no changes in the patient's vital signs. A sensory level of T8 was obtained. After 30 min, it was noted that the patient had a mild respiratory obstruction that was relieved by extension of the mandible. Of more serious import, the patient had become totally unarousable even by painful stimuli. Stimuli were both verbal and tactile and involved pinching and pricking the skin above the level of the block. The pupils were pinpoint in size. Naloxone hydrochloride, 0.4 mg intravenously in divided doses, was administered without change in the patient's mental state. Physostigmine hydrochloride, 1 mg intravenously, was subsequently administered. After several minutes the patient became disoriented and then minimally responsive for approximately 5 min. He then relapsed into his comatose state. During the periods of respiratory obstruction the oxygen saturation, monitored by pulse oximetry, frequently showed arterial oxygen saturations of below 70%, with improvement as soon as the respiratory obstruction was relieved. The naloxone and physostigmine were repeated, again without effect. At this time, other causes of his coma were considered. Serum electrolytes, blood glucose, and arterial blood gas tensions were measured. Serum electrolyte and glucose levels were normal. However, while breathing oxygen from a mask at a flow rate of 5 L/min and with an unobstructed airway, the arterial pH was 7.27, PO₂ 142 mm Hg, PCO₂ 60 mm Hg, and bicarbonate 27 mmol/L. Toxicology screen was positive only for a plasma meperidine level of 0.10 µg/ml, verifying that the correct dosage of premedication had been given (2). No other drugs (e.g., alcohol, other narcotics, phenothiazines, and sedatives) were found in the blood or in a urine assay carried out by the laboratory.

Received from the Department of Anesthesia, Stanford University School of Medicine, Stanford, California. Accepted for publication May 29, 1986.

Address correspondence to Dr. Samuels, Room S-278, Department of Anesthesia, Stanford University Medical Center, Stanford, CA 94305.

Neurologic consultation obtained after surgery found that apart from his obtundation, there was no neurologic deficit. A third dose of naloxone 0.4 mg was given this time with still no change in the level of consciousness. Computerized tomography of the brain showed no abnormality and over the ensuing hours the patient began to slowly awaken. That evening he was back to his awake state and the neurologic consult agreed with us that a sleep apnea study should be carried out. This involved monitoring the patient's electrocardiogram and oxygen saturation by ear oximetry during sleep, as well as respiratory airflow, thoracic respiratory effort, and abdominal respiratory effort to differentiate upper airway obstructive sleep apnea from central apnea. In addition, sleep stages were determined by electroencephalography, electromyography, and electrooculography to verify that the obstructive episodes did indeed occur during a period of sleep. These studies showed that in our patient sleep-induced obstructive apnea was associated with a decrease in arterial oxygen tension to 30 mm Hg, a decrease associated with multiple episodes of bradycardia and premature ventricular contractions. The cardiac arrhythmias were present only with the oxygen desaturations and were not felt to be secondary to underlying cardiac disease. The study was not influenced by the patient's previous anesthetic medications, as he was alert and oriented before and after the sleep study. Continuous positive airway pressure overnight eliminated his oxygen desaturations and arrhythmias.

Discussion with both the sleep studies physician and the ear, nose and throat physician the following morning led to the decision that, because of the severity of the cardiac disturbances associated with his sleep apnea-induced hypoxia, the patient should have a tracheostomy performed for long-term prophylaxis to prevent a possible sleep-induced cardiac death. Subsequently, the Food and Drug Administration approved the use of continuous positive airway pressure at night to treat this disorder. Because this had not been approved at the time of the case report, the patient underwent an uneventful tracheostomy with the use of local anesthesia. He returned to the orthopedic clinic two weeks after the surgery with both the fracture and tracheostomy sites in good condition. The patient failed to return to the clinic for further follow-up.

Discussion

The differential diagnosis of postoperative coma and prolonged emergence from anesthesia includes three major categories: drug interactions; metabolic disorders;

and neurologic injury. Coma secondary to drug interactions is commonly due to medication overdose or altered pharmacokinetics, including decreased metabolism or excretion. In the above case report both patient overdose and iatrogenic overdose were ruled out by intraoperative measurement of serum and urine drug levels and by the lack of a history of drug abuse.

Metabolic causes of prolonged emergence are numerous and include alterations in levels of serum electrolytes and glucose, and changes in acid/base status. Other metabolic causes include hypoxia, hypercapnia, and hepatic, renal, and endocrine disorders. Most of these possibilities were excluded as causes of this patient's failure to regain consciousness by results obtained from the laboratory studies.

A neurologic insult such as previous trauma, cerebral embolism or ischemia, or administration of neurotoxic drugs was considered in the diagnosis of coma in our patient. However, these were unlikely because of the patient's normal computerized tomography scan and the lack of focal findings on neurologic examination. In addition, arterial venous malformation and tumor were ruled out. It seemed likely that because of the patient's physical habitus and the clinical picture of recurrent obstruction, a likely diagnosis was that of sleep apnea (2). This diagnosis was subsequently confirmed by sleep apnea studies.

It has been known for some time that patients with sleep apnea may be very sensitive to drugs that depress the central nervous system (1). This sensitivity has been demonstrated as anything from mild respiratory obstruction to complete apnea and the need for a tracheostomy. Such airway obstruction is commonly amenable to simple mechanical measures. In our patient the spinal anesthesia decreased pain stimulus from his fractured tibia and allowed him to sleep in his usual sleep apnea state. The addition of a small premedication showed him to be extremely sensitive to small doses of sedatives, as has been reported in sleep-apnea patients. The combination of decreased sensory input and his sensitivity to the medications induced a comatose state. In our patient, the simple mechanical maneuver of chin extension relieved his obstruction but failed to reverse his coma. It seemed logical then to attempt to reverse the narcotic sedative combination with appropriate therapy, namely naloxone and physostigmine. Despite several doses of these two drugs the patient became only minimally responsive.

This case illustrates two points. One, which is becoming more widely appreciated, is that patients with sleep apnea are very sensitive to central nervous system-depressant drugs. Perhaps more important is the fact that unlike normal patients, in patients with sleep

Anesthetic Management of a Patient with Reactive Airway Disease for Carbon Dioxide Laser Debulking of a Laryngeal Tumor

Chester North, MD, PhD, Brian Marsh, MD, and Carol A. Hirshman, MD

The anesthetic management of a patient with reactive airway disease (1) and an obstructing lesion of the upper airway presents certain well-documented problems (1,2). When these two diseases coexist, potentially conflicting anesthetic requirements are present. We describe the anesthetic management of a patient with known reactive airway disease who presented with stridor and required urgent debulking of a large laryngeal tumor.

Case Report

A 65-yr-old woman with well-controlled hypertension, chronic obstructive pulmonary disease with a reversible reactive component, and a 2-yr history of progressive hoarseness was referred to our institution for laryngoscopy and carbon dioxide laser debulking of a laryngeal tumor. Six weeks before she had been admitted to another hospital in respiratory failure. Blood gases at that time revealed a PaO_2 of 42 mm Hg (while breathing room air), a PaCO_2 of 69 mm Hg and a pH of 7.26. Chest x-ray revealed a right lower lobe infiltrate and sputum samples grew out *Klebsiella pneumoniae*. She required antibiotics, intravenous aminophylline, tracheal intubation, and mechanical ventilation. Four weeks prior to the present admission, she was referred for persistent hoarseness to an otolaryngologist who discovered a mass in her neck. She underwent laryngoscopy and biopsy at another institution. During induction of anesthesia with oxygen and isoflurane by mask, supraventricular tachycardia developed. Her serum K^+ at that time was 2.0 mM/L. The diagnosis on discharge was squamous cell carcinoma of the right vocal cord.

Medications on admission to our institution included spironolactone, 25 mg twice a day, predni-

sone, 5 mg/day, alpramethyldopa, 250 mg three times a day, ranitidine, 150 mg/day, a long-acting theophylline preparation, 300 mg twice a day, metoprolol, 40 mg twice a day, and KCl 10%, one tablespoon four times a day.

Preoperative evaluation demonstrated a 50 kg non-cyanotic female who spoke in a whisper and had stridorous breathing at rest. The oropharynx appeared normal, the respiratory rate was 20 breaths per minute, and upon auscultation of the chest there were inspiratory and expiratory sounds in both upper and lower lung fields bilaterally. Arterial blood gas tensions were PaCO_2 36 mm Hg, PaO_2 92 mm Hg, and pH 7.43 while breathing room air. Serum K^+ was 4.4 mM/L, and serum theophylline level 18 mg/L. The electrocardiogram showed a normal sinus rhythm, and a CT scan of the larynx showed a laryngeal mass with subglottic and supraglottic extension.

After premedication with oral diazepam, 10 mg, the patient was brought to the operating room and 200 μg fentanyl were administered intravenously while the right naris was anesthetized with 5% cocaine. Lidocaine, 2 mg/kg intravenously, was administered followed by a continuous infusion of lidocaine at 50 mg/hr ($1 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{hr}^{-1}$). A transtracheal block was performed with 3 ml of 4% lidocaine and a nasotracheal intubation was performed over a fiberoptic bronchoscope (Model 118-5A, American Optical, Southbridge, MA) using a 6-mm inner diameter vinyl plastic endotracheal tube. No wheezing was audible. General anesthesia was then induced with 4 mg/kg thiopental and maintained with 50% nitrous oxide-50% oxygen-isoflurane. After laryngoscopy, the nasotracheal tube was removed under direct vision and the trachea reintubated by the oral route with a copper foil-wrapped 6.5-mm inner diameter endotracheal tube for carbon dioxide laser debulking. When this procedure was completed, a vinyl plastic oral endotracheal tube was substituted. Isoflurane and nitrous oxide were discontinued, but the lidocaine infusion and oxygen were continued and the patient was taken to the postanesthetic recovery area. Her trachea was

Received from the Department of Anesthesiology, Oregon Health Sciences University, Portland, Oregon. Accepted for publication May 19, 1986.

Address correspondence to Dr. Hirshman, Department of Anesthesiology, Oregon Health Sciences University, 3181 SW Sam Jackson Park Road, Portland, OR 97201.

extubated when she was fully awake. Mild inspiratory and expiratory sounds could be heard upon auscultation of the chest. The lidocaine infusion was discontinued. She recovered with no significant problems and was discharged home on the second postoperative day.

Discussion

This patient had long-standing, well-documented chronic obstructive pulmonary disease with a reactive component for which she was taking steroids and long-acting theophylline preparation. In addition, she had a laryngeal mass that extended supraglottically and subglottically causing stridor at rest.

In the preoperative evaluation of a patient with either upper or lower airway obstruction, spirometry may be helpful. In patients with mainly upper airway obstruction, marked linearity of the expiratory spirogram and a lack of response to bronchodilators are seen, whereas in patients with lower airway obstruction (reactive airway disease and emphysema) of similar severity, flow decreases as lung volume decreases. However, in our patient spirometry would have yielded little additional information (3,4) because we knew she had the mass. It was seen at surgery two weeks before and on tomograms of the larynx. Her serum theophylline level preoperatively was in the high therapeutic range and her dose of steroids had been increased. In the preoperative physical examination she appeared to have mainly upper airway obstruction. Inspiratory sounds were greater than expiratory sounds and were transmitted identically to all lung fields.

In this patient, anesthetic management, especially tracheal intubation, presented us with a dilemma. We had three possible choices: induction of anesthesia with an inhalation agent and intubation of the trachea after the patient was deeply anesthetized, intubation with the patient awake, or tracheostomy under local anesthesia.

The surgeons wanted to avoid a tracheostomy because of the possibility of seeding of tumor cells at the tracheostomy site because a radical neck dissection was anticipated.

Inhalation induction with oxygen and spontaneous respiration is the recommended management of a patient with reactive airway disease (1). However, the airway obstruction may worsen during induction and a real danger exists that bleeding, secretions, or edema may cause total obstruction (2), especially if intuba-

tion proves difficult. Hypoventilation with hypercarbia and cardiac arrhythmias are possible complications and had occurred during anesthesia two weeks previously at another institution.

An awake intubation runs the risk of precipitating severe bronchospasm in a patient with reactive airway disease (1). The endotracheal tube stimulates irritant receptors found beneath the airway epithelium, which initiates reflex bronchoconstriction (5). However, local anesthetics are effective for blocking this reflex (6). Therefore we elected to administer a bolus dose of lidocaine followed by a continuous infusion of lidocaine that was calculated to produce plasma lidocaine levels in the therapeutic range (7) while the patient was still awake and prior to placing the endotracheal tube.

We wanted to avoid direct laryngoscopy in this patient. Because blind nasal intubation can readily convert a partial obstruction to a total obstruction under these circumstances, we elected to perform the nasal intubation by means of a fiberoptic bronchoscope even though we knew we would have had to change to a tube suitable for carbon dioxide laser surgery after induction of anesthesia. We also elected to extubate this patient awake while continuing the lidocaine infusion.

The serious nature of both the asthma and the airway obstruction caused by the tumor necessitated a careful balance of the conflicting requirements of these two conditions in the anesthetic management of this patient.

The authors wish to thank Ms. Beth Sorenson for her assistance in typing and editing the manuscript.

References

1. Kingston HGG, Hirshman CA. Perioperative management of the patient with asthma. *Anesth Analg* 1985;63:844-55.
2. Donlon JV. *Anesthesia*. Volume 2. New York: Churchill Livingstone, 1981:1310-4.
3. Miller RD, Hyatt RF. Obstructing lesions of the larynx and trachea. *Mayo Clin Proc* 1969;44:145-61.
4. Pare PD, Donevan RE, Nelems JMB. Clues to unrecognized upper airway obstruction. *Can Med Assoc J* 1982;127:39-41.
5. Hirshman CA. Airway reactivity in humans: anesthetic implications. *Anesthesiology* 1983;58:170-7.
6. Downes H, Gerber N, Hirshman CA. IV lignocaine in reflex and allergic bronchoconstriction. *Br J Anaesth* 1980;52:873-8.
7. Greenblatt WJ, Bolognini V, Koch-Weser J, Harmatz JS. Pharmacokinetic approach to the clinical use of lidocaine intravenously. *JAMA* 1976;236:273-7.

Anesthetic Management of a Child with an Intratracheal Tumor

John G. Goode, MD, Ralph F. Wetmore, MD, and Thomas P. Keon, MD

Anesthesia for removal of a tracheal tumor or foreign body should be planned with the realization that life-threatening airway obstruction may be encountered. The management of such patients must include a thorough preoperative evaluation as well as a plan that anticipates the possible complications associated with induction of anesthesia. Our anesthetic management of a child for diagnostic endoscopy and surgical removal of a tracheal tumor is reported.

Case Report

An 8-yr-old, 25-kg boy was well until approximately 6 months prior to his admission to our hospital. During the previous six months he had been treated for increasingly frequent episodes of respiratory distress associated with respiratory tract infections. He was hospitalized on two occasions, once with a diagnosis of laryngotracheobronchitis and later with symptoms of asthma. After his second hospitalization, his symptoms of cough, noisy breathing, intermittent stridor, and expiratory wheezing persisted in spite of therapy that included theophylline, dexamethasone, diphenhydramine, and antibiotics. His symptoms continued to increase in severity with a decrease in exercise tolerance and intermittent nasal flaring. Chest x-ray showed hyperaeration of the right lower lobe. Further review of the chest films revealed a mass lesion in the distal trachea, which prompted computed tomography (CT) of the chest. The child's past history was otherwise negative; because he was adopted, the family history was not known.

Physical examination revealed a thin boy in no distress when sitting upright in bed or lying in the lateral position. When placed in the supine position, however, he became uncomfortable and tachypneic and developed retractions with utilization of his accessory

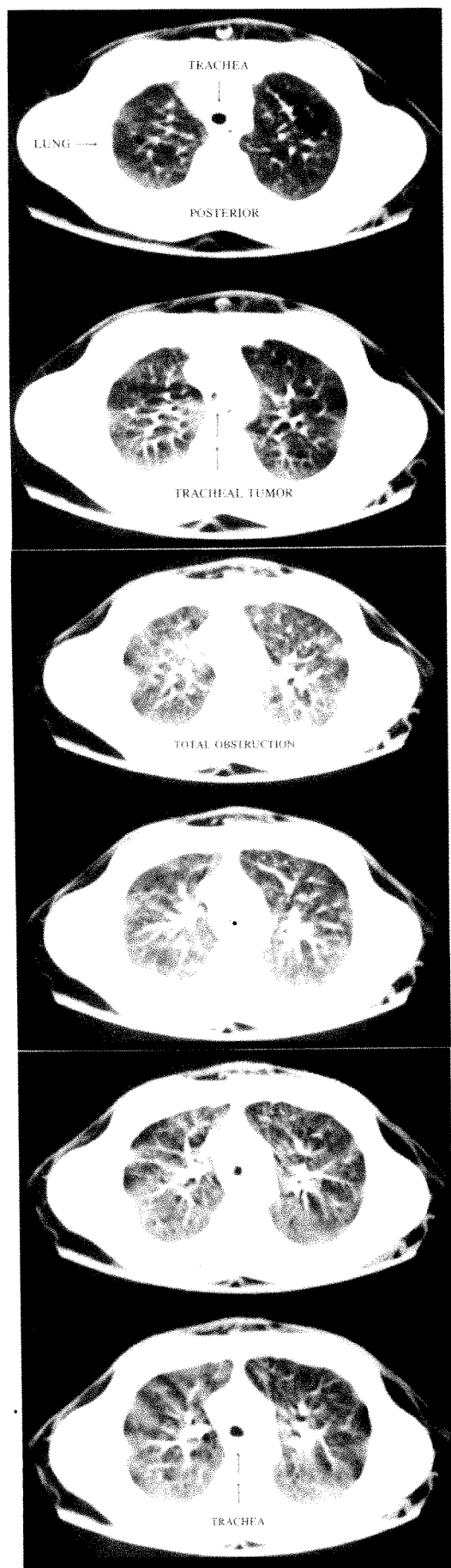
muscles of respiration. Prolonged, diffuse, high-pitched expiratory wheezes were heard over both lung fields and over the suprasternal notch. Examination of the nose, oral cavity, oropharynx, and neck was normal. Heart tones were of normal intensity with a regular rhythm, and no murmurs were detected. The remainder of his physical examination was normal.

Laboratory data included a hemoglobin of 13.5 g, white blood cell count of 8100, and platelet count of 420,000. Serum electrolytes, urea nitrogen, and creatinine levels were normal, as was urinalysis. A CT scan of the chest confirmed a mass in the distal trachea approximately 1 cm above the carina with almost complete obstruction of the airway (Fig. 1). The proximal trachea was unobstructed, and the carina and main bronchi were clear. Pulmonary function studies and a flow volume loop revealed expiratory flow rates to be 15–20% of predicted values. Residual lung volume was measured as 300% of the predicted value, confirming significant air trapping, and his maximum voluntary ventilation (MVV) was 16% of the predicted value.

Preoperatively the child's parents were advised that the risk of anesthesia was significantly increased, and we described the plan we would implement to the parents. The child was reassured and advised that we would begin an intravenous for the administration of medication until he was drowsy. He understood that we would continue to talk to him during the initial endoscopy of the trachea. Premedication consisted of atropine (0.02 mg/kg) orally 1 hr prior to induction. The child was placed on the operating room table with the back elevated 45°. Electrocardiographic leads, blood pressure cuff, pulse oximeter sensor, and a precordial stethoscope were applied. Incremental doses of diazepam (total 0.3 mg/kg) and fentanyl (total 2 µg/kg) were administered until he was drowsy but still responsive to commands. Topical 4% cocaine was applied to the nasal mucosa, and bilateral superior laryngeal nerve blocks were performed with 1 ml of 2% lidocaine. While 100% oxygen was administered using a clear face mask, an Olympus BF-3CA pediatric bronchoscope was passed through a small hole in the face mask and through the nose into the hypophar-

Received from the Department of Anesthesia and Critical Care and the Division of Otolaryngology and Human Communication, Children's Hospital of Philadelphia, Philadelphia, Pennsylvania. Accepted for publication May 5, 1986.

Address correspondence to Dr. Keon, Department of Anesthesia and Critical Care, The Children's Hospital of Philadelphia, 34th and Civic Center Blvd, Philadelphia, PA 19104.



ynx. The fiberscope was positioned at the larynx, while 3 ml of 2% lidocaine was sprayed into the trachea through the suction channel of the fiberscope. The bronchoscope was then passed into the trachea with minimal coughing and continued excellent patient cooperation. In the distal trachea, a large mass that appeared to be a granuloma almost completely occluded the airway. At this point, consideration was given to terminating the examination and arranging for extracorporeal oxygenation capability and an extratracheal approach to the tumor. On the other hand, if the fiberscope could be passed beyond the tumor with visualization of the carina, then a rigid bronchoscope or small endotracheal tube should be able to pass the lesion. The fiberoptic bronchoscope was passed easily with visualization of a normal carina. The decision was made to induce general anesthesia for insertion of the rigid bronchoscope.

The fiberoptic bronchoscope was removed, and halothane in increasing concentrations with 100% oxygen was administered. Spontaneous ventilation was maintained, and use of 15–20 cm water end-expiratory pressure dramatically improved air entry. A 4-mm Storz-Hopkins bronchoscope was introduced and passed beyond the lesion, permitting optimal ventilation of both lungs. Surgical resection of the lesion was completed through the bronchoscope with continued ventilation of the patient through the 15-mm side arm attachment. The patient was intubated with a 6.0-mm endotracheal tube at the termination of the procedure. The tracheobronchial tree was suctioned and the patient extubated awake with active airway reflexes.

Histologic examination of the tumor revealed a neurofibroma. Careful postoperative examination failed to reveal any stigmata of neurofibromatosis.

Discussion

Distal tracheal obstruction, whether due to foreign body, stenosis, or tumor, is particularly treacherous for both the anesthesiologist and the surgeon. The lesion may not allow passage of either an endotracheal tube or rigid bronchoscope beyond it for ventilation. Likewise, an emergency tracheostomy will not improve a distal tracheal obstruction. Induction of general anesthesia may be associated with increasing airway obstruction that cannot be relieved by positive pressure ventilation. Both emergency extracorporeal oxygenation (1) and cardiopulmonary bypass

Figure 1. Computed tomography of chest. Cuts were made at 5-mm intervals from 3.5 cm above the carina caudad to 1.5 cm above the carina. The third cut from the top reveals occlusion of the trachea by neurofibroma.

have been described in the anesthetic management of surgical procedures on the lower trachea (2,3,4,5). In this case the preoperative diagnosis was uncertain, but the CT scan revealed almost total occlusion of the trachea 1 cm above the carina (Fig. 1). The flexible fiberoptic bronchoscope permitted a functional evaluation of the lesion without the induction of general anesthesia and confirmed our ability to bypass the lesion with a small tube. If we had encountered difficulty during the examination or were unable to easily bypass the lesion, we had planned to then arrange for the institution of extracorporeal circulation prior to the induction of anesthesia. In addition, fiberoptic examination in the awake patient confirms the presence of normal airway anatomy both proximal and distal to the tracheal lesion.

Grillo states that it is almost always possible to intubate the patient beyond an obstructing tumor unless it is at the carina, because the tube can be passed along the uninvolved wall of the trachea (6). However, Parish et al. reported a 34-yr-old adult in whom neither a bronchoscope nor biopsy forceps would pass a tracheal tumor located 1.5 cm above the carina. Fortunately ventilation was possible with high inflating pressures (70-90 cm of water) (7). We suggest that it is advantageous to determine whether a tube can be passed beyond the lesion prior to the induction of general anesthesia. This approach permits time for the preparation of cardiopulmonary bypass and planning for a major surgical procedure. Maharaj et al. reported a case where the institution of emergency extracorporeal oxygenation prior to induction of anesthesia in a patient with severe tracheal stenosis caused by an intratracheal foreign body proved life-saving (1). An attempt at ventilation after induction and during extracorporeal oxygenation proved almost impossible; in spite of high inflation pressures there was very little chest movement or air entry. Lippmann and Mok (8) described an adult with a distal tracheal cylindroma in whom sudden airway obstruction occurred after 1 hr of anesthesia. Fortunately the chest was open, permitting immediate intubation of the bronchus and ventilation of this patient. Dodge et al. (9) reported a patient with a lower tracheal mass in whom the femoral artery and vein were exposed under local anesthesia in preparation for extracorporeal oxygenation if needed. This proved unnecessary, as general anesthesia was completed without major difficulty. Nevertheless, intermittent ball-valve type obstruction occurred prior to opening of the trachea and resection of the tumor.

Patients with tracheal tumors frequently present with symptoms suggestive of small airway disease such as asthma, and they are often treated with bronchodilators and steroids (7). Obstruction usually pro-

gresses until the patient's compensatory mechanisms begin to fail and signs of increased work of breathing are observed. Signs of increased work of breathing and airway obstruction at rest suggest that marked reduction in airway diameter is present. A flow volume loop will reveal an expiratory plateau, indicating reduced peak expiratory flow. Tracheal tomography and computed tomography may prove helpful in delineating the extent of airway involvement.

Primary tumors of the trachea are rare in the pediatric age group. The most common is the papilloma, usually seen in association with laryngeal papillomatosis (10). Neurofibromas of the trachea are extremely rare, with only five cases reported in the world literature as of 1983 (11). Only one of these cases was associated with neurofibromatosis (11). In previous reports of neurofibromas of the trachea, a variety of surgical approaches were employed. At least one other tumor was excised endoscopically, as in the current case (12). External approaches to the trachea through either the neck or chest were employed in other reports.

In summary, the anesthetic management of lesions of the distal trachea include the following principles: Preoperative evaluation should include chest radiographs and CT of the chest. Pulmonary function and flow volume loop studies are useful in determining the degree of obstruction. Sedative premedication is avoided, but a preoperative anticholinergic is useful in reducing airway secretions. The maintenance of the patient's preferred position (avoiding the supine position), small incremental doses of sedation, and topical anesthesia permit careful examination of the tracheal lesion prior to the induction of general anesthesia. If the establishment of a satisfactory airway does not seem likely, then an arrangement for utilizing extracorporeal oxygenation prior to induction of general anesthesia must be made. Close cooperation between the anesthesiologist and the surgeon and careful evaluation and planning are crucial in caring for patients with distal tracheal obstruction.

References

1. Maharaj R, Whitton I, Blyth D. Emergency extracorporeal oxygenation for an intratracheal foreign body. *Anaesthesia* 1983;38:471-4.
2. Sadony V, Schramm G, Doetsch N. Management of extensive lesions of the lower trachea using emergency cardiopulmonary bypass. *Thorac Cardiovasc Surg* 1979;27:195-8.
3. Woods F, Neptune W, Palatchi A. Resection of the carina and main stem bronchi with the use of extracorporeal circulation. *New Engl J Med* 1961;264:492-4.
4. Adkins P, Izawa E. Resection of tracheal cylindroma using cardiopulmonary bypass. *Arch Surg* 1964;88:405-9.
5. Neville WE, Thomason RD, Peacock H, et al. Cardiopulmonary bypass during non-cardiac surgery. *Arch Surg* 1966;92:576-87.

High Frequency Positive Pressure Ventilation during General Anesthesia for Extracorporeal Shock Wave Lithotripsy

Azriel Perel, MD, Benjamin Hoffman, MD, Dov Podeh, MD, and
Joseph T. Davidson, MD, FFARCS

Extracorporeal shock wave lithotripsy (ESWL), a non-invasive treatment for renal calculi, achieves contact-free destruction of urinary stones through extracorporeally generated shock waves (1,2). The patient undergoing ESWL requires anesthesia, mainly because the shock waves (up to 2000 per treatment) are very painful. Also, accurate placement of the focus of maximal energy of the shock waves on the stone is vital for a successful procedure, and movement may displace the stone from that focus, leading to unnecessary trauma to adjacent organs, as well as partial or no disintegration of the stone itself. Both general and regional anesthesia are being used for ESWL (1,3). However, during either spontaneous or conventional mechanical ventilation, the diaphragmatic movements drive the stone up and down along a vertical axis, causing a proportion of the shock waves to miss the stone altogether. This suggested the use of high frequency jet ventilation (HFJV) at a rate of 100–300 breaths/min as the preferred mode of ventilation during anesthesia for ESWL (4,5), because the stone remains virtually stationary due to the low tidal volumes used in HFJV (4,6,7).

However, most anesthesiologists would be hesitant to use HFJV during ESWL, because this is still an unconventional and somewhat unpredictable ventilatory mode. Moreover, in most places special HFJV ventilators would have to be purchased and used for the first time. We have thus employed a conventional anesthesia ventilator for the delivery of high-frequency positive pressure ventilation (HFPPV) during anesthesia for ESWL. A ventilatory rate of 80 breaths/min with a tidal volume of approximately 3

ml/kg seems to be both effective and safe for this procedure.

Methods and Subjects

Thirty patients with nephrolithiasis in the upper urinary tract were anesthetized for ESWL. These patients included 21 men and nine women, who had a mean (\pm SD) age of 42.0 ± 11.4 yr and a mean weight of 73.1 ± 12.9 kg. Nineteen patients were ASA class I, 10 patients were ASA class II, and one patient was ASA class III. No premedication was given. After the insertion of a peripheral intravenous line, patients received 0.05 mg of fentanyl, followed by 1 mg of pancuronium.

After preoxygenation, a sleep dose of thiopental (4 mg/kg) and 1.5 mg/kg succinylcholine were administered, and tracheal intubation was performed. After an additional dose of pancuronium (up to 1 mg/15 kg), the patients were ventilated with a Siemens Servovent D-900 ventilator, using 50% N₂O and 50% oxygen with 0.6–1.2% halothane. Minute ventilation was set at $250 \text{ ml} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ at a preliminary rate of 80 breaths/min.

The patients were then transferred to the hydraulic stretcher and immersed in the half-sitting position in the water bath. After positioning and before starting the procedure, ventilation was temporarily changed to a ventilatory rate of 20 breaths/min, creating a tidal volume of 12.5 ml/kg for 10 min. At this point, movement of the main stone during ventilation was measured on the fluoroscopy screen. The patient was then ventilated at a rate of 80 breaths/min, and stone movement was again measured. Expired tidal volume and peak and mean airway pressures were recorded from the ventilator. In 10 patients "true" expired tidal volume was also recorded from a Wright spirometer mounted on the endotracheal tube. End-tidal CO₂ (PETCO₂) tension was continuously displayed by a Datex CO₂/O₂ analyzer, the sampling tube attached to

Received from the Department of Anesthesiology and Urology, Hebrew University, Hadassah Medical School, Hadassah Hospital, Jerusalem, Israel. Accepted for publication June 18, 1986.

Address correspondence to Dr. Perel, Department of Anesthesia, Hadassah Medical Center, P.O. Box 12000, Jerusalem, Israel 91120.

the oral port of the endotracheal tube. As measurement of P_{ETCO_2} becomes inaccurate during high frequency ventilation (8,9), we briefly reduced the rate to 20 breaths/min and recorded the P_{ETCO_2} of the first expired breath. Arterial blood gas tensions were measured at the same time. During ESWL ventilation was also changed once to a rate of 120 breaths/min for 10 min to determine whether a higher ventilatory rate would provide better conditions for ESWL. At the end of the procedure, halothane and N_2O were discontinued, muscle paralysis reversed with prostigmine (2.5 mg) and atropin (1 mg), and the patients were extubated and transferred to the recovery room.

We have used the Student's paired *t*-test to compare respiratory parameters at rates of 80 and 120 breaths/min ($P < 0.05$ was considered significant), and to compare stone movements at rates of 20, 80, and 120/min ($P < 0.01$ was considered significant due to multiple comparisons).

Results

As the set minute volume on the Servovent ventilator remained unchanged during the procedure (17.94 ± 3.66 L/min, mean \pm SD), the lower rate of 80 breaths/min produced tidal volumes (about 3 ml/kg) that were higher than those at 120 breaths/min (about 2 ml/kg) (Table 1). These larger tidal volumes were also accompanied by larger peak and mean airway pressures (Table 1).

End-tidal and arterial CO_2 tensions were significantly higher and pH significantly lower at a rate of 120 breaths/min (Table 2). However, patients were somewhat hyperventilated at both rates, and in no case was the $PaCO_2$ above 40 mm Hg. Mean large-breath-end-tidal and mean arterial CO_2 tensions were similar to each other for the whole group (Table 2), although there were differences of up to 10 mm Hg between simultaneous individual measurements. There was no significant difference in the mean PaO_2 between 80 and 120 breaths/min (Table 2), although some patients did show changes in both directions when switched from one rate to another. The lowest PaO_2 recorded was 71 mm Hg ($FI_{O_2} = 0.5$), but in most patients PaO_2 values were well above 100 mm Hg.

Mean stone movement on the fluoroscope during ventilation with a tidal volume of 12.5 ml/kg and a rate of 20 breaths/min was 17.8 ± 8.8 mm on the vertical axis (range 9–48 mm). Mean stone movement during ventilation with a rate of 80 and 120 breaths/min was 4.7 ± 1.8 mm (range 1.5–10 mm) and 1.2 ± 0.9 mm (range 0–3 mm), respectively. These values were statistically different from each other.

Table 1. Tidal Volume and Airway Pressures during HFPPV

Rate (breaths/min)	Expired tidal volume (ml)	Peak airway pressure (mm Hg)	Mean airway pressure (mm Hg)
80	206.0 ± 34.3	24.0 ± 7.7	7.3 ± 2.4
120	$134.4 \pm 22.2^*$	$20.9 \pm 5.9^*$	$6.0 \pm 1.8^*$

Values are expressed as mean \pm SD.

* $P < 0.001$ compared with 80 breaths/min.

Discussion

Our results, as well as those of others (4,6,7), show that a high-frequency low-tidal-volume ventilatory technique significantly reduces kidney stone movement during ESWL, as compared to conventional mechanical ventilation. Mean stone movement on the fluoroscope during conventional ventilation was reported to be about 30–32 mm (6,7) as opposed to about 2.5 mm during HFJV with rate of 100–300 breaths/min (6,7). We have found mean stone movement to be 18 mm during conventional ventilation, as opposed to 4.7 mm on HFPPV of 80 breaths/min, and 1.2 mm on HFPPV of 120 breaths/min.

The claimed superiority of a ventilatory technique that minimizes stone movement is based on some theoretical considerations. One analysis shows that if the vertical displacement of the stone is 32 mm, and if the vertical length of the maximal energy field is 12 mm, the stone would stay within this field only 30–50% of the time (4). This would make ESWL less effective, as more time and shock waves will be required to disintegrate the stone. Minimizing stone movement would theoretically reduce the number of shock waves necessary for stone breakdown, prevent unnecessary trauma to surrounding tissues, and obviate the need to repeat the procedure if the stone(s) have not been effectively crushed within the allowed 2000 shock waves of the first ESWL. A decrease in the number of required shock waves may also decrease the cost; each spark plug, of which an average of two per treatment are used, costs \$250.

Recently, it has been reported that a reduction in the required number of shock waves was indeed possible with HFJV, as well as the use of fewer electrodes and lower intensity shock waves (7). However, a definitive study proving that reducing stone movement is associated with a significant decrease in the number of shock waves required for stone breakdown has not yet appeared. This stems in part from the fact that the endpoint of the treatment cannot be determined arbitrarily and in part from the fact that stone breakdown is difficult to quantify. Moreover, as a further

Table 2. Arterial Blood Gas Tensions and End-Tidal PaCO_2 during HFPPV

Rate (breaths/min)	PaO_2 (mm Hg)	PaCO_2 (mm Hg)	PET_{CO_2} (mm Hg)	pH
80	144.1 ± 62.2	26.4 ± 3.6	25.6 ± 4.5	7.51 ± 0.04
120	137.0 ± 48.2	31.2 ± 4.5^a	29.6 ± 6.2^a	7.47 ± 0.05^a

^a $P < 0.001$ compared with 80 breaths/min.

destruction of the stone into fine grains facilitates its excretion, there is a tendency to use more shock waves even when the stone disintegrates relatively early.

There are other considerations, however, which suggest that the value of minimizing stone movement may be exaggerated. All reported stone movement data were taken from the fluoroscopy screen which produces a 2–2.5-fold magnification of the stone. The actual magnification factor depends on patient size, positioning of the image intensifier, and the electronic magnification factor of the screen itself (M. J. Dod, R. Naylor; Dornier Industries, personal communication). Thus even though the magnification is identical during the various modes of ventilation, it is possible that the importance of stone movement during conventional ventilation is overestimated. It also seems that although the dimensions of the maximal energy field are only about 1 cm^3 , this field is surrounded by concentric elliptical lesser energy fields that progress in the direction of the blast path. The time spent by the stone within an effective energy field would depend on its range of movement, the ratio between duration of inhalation and exhalation, the angle of the axis of the stone movement to the blast path, and the dimensions of the stone itself.

If the importance of preventing stone movement has been overestimated, then the choice of anesthetic technique should not be influenced by this consideration. Indeed, it seems that regional anesthesia with spontaneous breathing (3) is the anesthetic method of choice in many medical centers. The regional technique offers effective anesthesia and probably leads to a more efficient patient turnover in the usually busy ESWL setting.

When a general anesthetic for ESWL is chosen for medical indications, patient preference or considerations of stone movement (e.g., small stones where acute focusing of the epicenter of the shock waves might present a problem in the presence of excessive movement), we suggest that HFPPV and conventional anesthesia ventilators should be employed. Although HFJV has been successfully applied during ESWL (4,6,7), this mode of ventilation presents a number of problems. Monitoring of simple ventilatory parameters such as tidal volume, airway pressure, and PET_{CO_2} is usually impossible during HFJV. As

the entrained portion of the tidal volume, as opposed to the jet volume, carries the anesthetic inhalation agent, the overall concentration of the anesthetic gas cannot be accurately controlled (4,7). This drawback probably led some HFJV users to employ intravenous anesthesia for ESWL (6). Also, the open nature of the HFJV system dictates the use of high flows of gas that are both wasteful and difficult to effectively scavenge. Thus HFJV might not be considered a safe and comfortable mode of ventilation by anesthesiologists who have not used it previously. Its present use in adults in the US is still restricted by the FDA to laryngoscopies or bronchopleural fistulas.

On the other hand, volume-controlled HFPPV, as used in our study, is widely available and has been recommended as a safe and accurate ventilatory mode using both low-compression (10) and conventional (11, 12) ventilators. Most current conventional anesthetic ventilators can deliver tidal volumes of 3 ml/kg at a rate of 80 breaths/min, which are the ventilator setups that we found to be safe as well as effective in minimizing stone movement. A ventilatory rate of 120 breaths/min did not offer any significant advantage over a rate of 80 breaths/min, and indeed, most conventional ventilators cannot deliver this rate anyway. Because low tidal volumes may lead to decrease in FRC and hypoxemia, we consider the use of 50% oxygen, as well as intermittent large breath, prudent in HFPPV. We further recommend intermittent monitoring of end-tidal CO_2 by the occasional introduction of a large mechanical or manual inhalation.

References

1. Chaussy CH. Extracorporeal shock wave lithotripsy. New aspects in the treatment of kidney stone disease. Basel: Karger, 1982: 98–9.
2. Miller K, Fuchs G, Rassweiler J, Eisenberger F. Financial analysis, personnel planning and organizational requirements for the installation of a kidney lithotripter in a urologic department. *Urol* 1984;10:217–21.
3. Duvall JO, Griffith DP. Epidural anesthesia for extracorporeal shock wave lithotripsy. *Anesth Analg* 1985;64:544–6.
4. Schulte am Esch J, Kochs E, Meyer WH. Zum Einsatz von high frequency jet ventilation bei der extrakorporalen Stosswellenlithotripsie. *Anaesthesist* 1985;34:294–8.
5. Carlson CA, Gravenstein JS, Banner MJ, Boysen PG. Moni-

- toring techniques during anesthesia and HFJV for extracorporeal shock-wave lithotripsy. *Anesthesiology* 1985;63:A178.
6. Carlson CA, Boysen PG, Banner MJ, Gravenstein JS. Conventional vs high frequency jet ventilation for extracorporeal shock-wave lithotripsy. *Anesthesiology* 1985;63:A530
 7. Schulte am Esch J, Kochs E, Meyer WH. Improved efficiency of extracorporeal shock wave lithotripsy during high frequency jet ventilation. *Anesthesiology* 1985;63:A177.
 8. Colgan FJ, TenEyck LG, Sawa T. Ventilation requirements during high frequency ventilation. *Crit Care Med* 1983;11:173-6.
 9. Mihm FG, Feeley TW, Rodarte A. Monitoring end-tidal carbon dioxide tensions with high frequency jet ventilation in dogs with normal lungs. *Crit Care Med* 1984;12:180-2.
 10. Sjöstrand UH. Development of high frequency positive pressure low-compression ventilation. *Int Anesthesiol Clin* 1983;21:11-32.
 11. Babinsky MF, Smith RB, Sjöstrand UH. Volume controlled high frequency positive pressure ventilation for upper abdominal surgery. *Anaesthesia* 1985;40:619-23.
 12. Abu-Dbai J, Flatau E, Lev A, Kohn D, Monis-Hass I, Barzilay E. The use of conventional ventilators for high frequency positive pressure ventilation. *Crit Care Med* 1983;11:356-8.

Postoperative Seizures after Isoflurane Anesthesia

Janet L. Harrison, MD

Intraoperative seizure activity during general anesthesia with isoflurane has been reported by Hymes (1). In the reported case, increased muscle tone progressed to sustained myoclonus of the lower extremities 2 hr after induction of anesthesia. The patient's vital signs remained unchanged, and laboratory evaluation, including arterial blood gas tensions and serum levels of electrolytes and calcium, was normal. The myoclonus persisted into the recovery period in the presence of an apparently normal level of consciousness.

The proposed role of isoflurane as the etiologic agent of the seizures in the patient described by Hymes has been questioned by Keats (2) on the basis that the patient had received multiple drugs including diazepam, morphine, glycopyrrolate, fentanyl, *d*-tubocurarine, thiopental, succinylcholine, nitrous oxide, and isoflurane. The present report describes postoperative myoclonus and seizure-like activity in a patient who received only thiopental, nitrous oxide, oxygen, and isoflurane.

Case Report

A 69-yr-old, 79-kg female was scheduled for arthroscopy as an outpatient. Medical history included degenerative joint disease, exogenous obesity, and hypertension treated with hydrochlorothiazide every other day. She had no allergies. One prior anesthetic for oophorectomy and appendectomy was reported to be ether, in 1943. Preoperative laboratory data included hemoglobin 14.5 gm % (9.0 mmol/L) and normal levels of serum electrolytes. The electrocardiogram (ECG) showed a sinus rhythm with an interventricular conduction delay. The patient had a history of low back pain and requested general rather than regional anesthesia.

The patient was brought to the operating room

without premedication. An intravenous infusion was begun, and monitoring of blood pressure (BP), ECG, and temperature was started, together with use of a precordial stethoscope and an oxygen analyzer. BP was 140/80 mm Hg; heart rate (HR) was 76 beats/min. The patient was given thiopental, 350 mg intravenously (IV). Anesthesia was maintained with nitrous oxide 3 L/m, oxygen 2 L/m, and isoflurane 1.5%, decreased to 1% 20 min after induction. After induction an oral airway was inserted and respirations were assisted easily. Inspired oxygen was 39–41%. Blood pressure ranged from 120–160/68–80 mm Hg, and HR ranged from 70 to 76 beats/min intraoperatively.

The arthroscopy was performed with a tourniquet time of 40 min, and the patient was taken to the recovery room 70 min after entering the operating room. On admission to the recovery room, BP was 130/70 mm Hg, HR 72 beats/min, and respirations 16 breaths/min. Oxygen 40% was administered by face mask. Five minutes after arrival, the patient removed her oral airway and when asked how she felt, replied "fine."

The patient continued to be responsive until 18 min after admission to the recovery room, at which time she developed myoclonic-type movements of her shoulders and arms. No rigidity was noted. She was not responding to verbal stimuli. Blood pressure was 142/90 mm Hg, and HR was 72 beats/min. Diazepam 10 mg IV stopped the myoclonus. She showed no response to deep pain, but vital signs, including temperature, remained unchanged. An arterial blood sample obtained while she was breathing 40% O₂ by mask showed a pH of 7.38, PO₂ 86 mm Hg, PCO₂ 45 mm Hg, HCO₃⁻ 26 mEq/L, and O₂ saturation 96%. Other laboratory measurements remained normal; sodium 147 mEq/L, potassium 3.7 mEq/L, magnesium 2.2 mg/dl (0.91 mmol/L), calcium 9.0 mg/dl (4.5 mmol/L), BUN 17.8 mg/dl (6.35 mmol/L), and glucose 133 mg/dl (7.4 mmol/L). The ECG was unchanged. Pupils were small, equal, and reactive; deep tendon reflexes were normal; Babinski reflexes were absent. There was no bowel or bladder incontinence and no lateralization of seizure activity.

Received from the Department of Anesthesia, Audrain Medical Center, Mexico, Missouri. Accepted for publication June 26, 1986.

Address correspondence to Dr. Harrison, Department of Anesthesiology, Audrain Medical Center, 620 E. Monroe, Mexico, MO 65265.

Thirty minutes later, the upper extremity twitching resumed and was again treated with IV diazepam in increments up to 10 mg. After another 30 min, myoclonus again resumed and this time was treated with diphenylhydantoin slowly IV to a total dose of 400 mg.

Twenty minutes later the patient still had slight myoclonus but was responding to verbal stimuli. One hour later myoclonus was absent but could be reproduced by physical stimulation of the extremities. She was observed in the recovery area for one more hour before being transferred to the ward. No further anticonvulsants were given.

The patient subsequent to leaving the recovery room did well and was discharged home the following day. She had no recall of RR events. A followup EEG was normal. She was advised to inform anesthesiologists caring for her in the future of these happenings.

Discussion

Myoclonic seizures usually present as part of the symptom-sign complex of genetically determined epilepsies; however, myoclonus can occur as a result of diffuse encephalopathies and head injury. Bilateral or focal myoclonic jerks commonly occur in postanoxic encephalopathy or with other metabolic derangements of the brain (3). Although nonepileptic seizures in the perioperative period are rare, the most frequent causes are hypoxia and metabolic disturbances, in-

cluding hypocalcemia, hypoglycemia, hypomagnesemia, and hyponatremia. Our laboratory data failed to demonstrate any such abnormalities.

Other possible causes include malignant hyperthermia, pheochromocytoma, porphyria, thyrotoxic storm, subarachnoid or intracerebral hemorrhage, and alcohol or barbiturate withdrawal; however, the patient exhibited no change in vital signs or other signs of these disorders.

Factors in this patient similar to those in the case described by Hymes include myoclonic-type movements of extremities that were increased by stimulation, normal laboratory values, unchanged vital signs, lack of seizure history, and the absence of urinary or stool incontinence. The present patient developed myoclonus in the recovery period (90 min after induction), whereas Hymes's patient developed myoclonus and rigidity 2 hr after induction while still receiving isoflurane; however, his seizure-like activity also persisted into the recovery period. In light of these similarities, this case gives further support to isoflurane as a rare but possible cause of seizure-like activity.

References

1. Hymes JA. Seizure activity during isoflurane anesthesia. *Anesth Analg* 1985;64:367-8.
2. Keats AS. Seizures from isoflurane? *Anesth Analg* 1985;64:1225-6.
3. Wilder BJ, Schmidt RP. Current classification of epilepsies. *Postgrad Med* 1985;77:188-99.

Refractory Bradycardia after Reversal of Muscle Relaxant in a Diabetic with Vagal Neuropathy

Anastasios N. Triantafyllou, MD, Kentaro Tsueda, MD, Jeffrey Berg, MD, and T. Jeffery Wieman, MD

The incidence of autonomic neuropathy is high in diabetic patients (1). Indeed, there is evidence to suggest that sudden deaths in diabetics may not always be due to silent myocardial infarction but may also be due to autonomic neuropathy (2). Recently, unexpected and sudden cardiorespiratory arrests in the perioperative period have been documented in patients with advanced diabetes (3,4). Abnormal autonomic nervous system function was implicated in these arrests.

We report an elderly diabetic with advanced peripheral somatic neuropathy who developed a progressive bradycardia after intravenous (IV) injection of neostigmine and glycopyrrolate for reversal of a muscle relaxant. The patient had to be resuscitated with external cardiac massage and intravenous epinephrine. Cardiac autonomic nervous system function tests performed after the operation were consistent with severe damage of the cardiac vagus nerve.

Case Report

A 61-yr-old man, 175 cm in height and weighing 75 kg, was admitted for treatment of an infected left foot that developed after stepping on a thumbtack one week prior to admission. The patient was a Type II diabetic of approximately 15 yr duration but had not visited the clinic regularly. The patient had a history of hypertension, congestive heart failure, peripheral vascular disease, chronic renal failure, and proliferative retinopathy, but he denied symptoms suggestive of autonomic neuropathy, e.g., gastroparesis, intermittent diarrhea, abnormal sweating, orthostatic hypotension, and urinary bladder or sexual dysfunction.

The patient had been active, working until the onset of his current illness, and was not taking any medication at the time of admission. Because of his refusal to take subcutaneous insulin, the patient was treated with glipizide, 20 mg twice per day, which stabilized his blood sugar levels in the range of 200–240 mg% (11.1–13.3 mmol/L).

Pertinent findings on physical examination included bilateral retinal scars due to laser surgery for his retinopathy and peripheral somatic neuropathy involving both lower extremities and both upper extremities. Pain perception was impaired below the mid-thigh level in the lower extremities and below the elbow in the upper extremities. Deep tendon reflexes were weak in the upper extremities and absent at the knees and ankles. Arterial blood pressure was 160/90 mm Hg, and heart rate was 102 beats/min. The hemoglobin was 9.7 g/dl (6.0 mmol/L), and the serum potassium 4.4 mmol/L. The blood urea nitrogen and creatinine values were 28 and 2.1 mg/dl (1000 and 186 mmol/L), respectively. The creatinine clearance was 43.1 ml/min (0.72 ml/sec). The urinalysis showed 3+ proteinuria. The ECG showed sinus tachycardia (103 beats/min), with diffuse nondiagnostic T-wave abnormality.

The infection did not improve after treatment with a short course of antibiotics, and the area became gangrenous. A transmetatarsal amputation was performed in an attempt to save the heel 4 days after admission. The patient tolerated the procedure well under spinal anesthesia with lidocaine, 60 mg. Arterial blood pressure remained stable at 145/85 mm Hg, and heart rate remained at 104 beats/min during the 45-min procedure. Because of poor control of the infection, the patient was brought back to the operating room for a below-knee amputation 5 days after the transmetatarsal amputation. He tolerated the 55-min procedure well under spinal anesthesia with hyperbaric tetracaine, 8 mg. The arterial blood pressure ranged from 160/95 to 150/90 mm Hg. The heart rate

Received from the Departments of Anesthesiology and Surgery, Humana Hospital University, University of Louisville School of Medicine, Louisville, Kentucky. Accepted for publication June 26, 1986.

Address correspondence to Dr. Tsueda, Department of Anesthesiology, University of Louisville, Louisville, KY 40292.

remained unchanged at 106 beats/min. One week later, he returned for debridement of the stump, but at this time, repeated attempts at spinal anesthesia failed. The procedure was done under local anesthesia. Because of continued infection, he was scheduled for revision of the below-knee amputation to above-knee amputation 19 days after admission. This time the patient refused spinal anesthesia. The hemoglobin was 8.7 g/dl (5.4 mmol/L). The arterial blood gas tensions with an $F_{I_{O_2}}$ of 0.21 were: pH 7.35, P_{aO_2} 70 mm Hg, and P_{aCO_2} 38 mm Hg. Premedication was not given.

Anesthesia was induced with thiopental, 250 mg IV, after *d*-tubocurarine, 3 mg IV. Tracheal intubation was facilitated with succinylcholine, 100 mg. Anesthesia was maintained with fentanyl, 250 μ g, and isoflurane, 0.25%, with 50% nitrous oxide. The isoflurane concentration was occasionally increased to 0.5% when the arterial blood pressure increased. Skeletal muscle relaxation was provided with vecuronium, 6 mg. The degree of muscle relaxation was monitored with a nerve stimulator. Respiration was mechanically controlled. Arterial blood pressure decreased from the preinduction value of 180/95 mm Hg to 150/90 mm Hg and remained stable at that level during the entire operation, which lasted 2 hr. Heart rate ranged from 104 to 96 beats/min. Approximately 1 hr after the induction of anesthesia, arterial blood tensions ($F_{I_{O_2}}$ of 0.5) were as follows: pH 7.43, P_{aO_2} 126 mm Hg, and P_{aCO_2} 35 mm Hg.

Toward the end of the operation, vecuronium was reversed with a mixture of neostigmine, 3 mg, and glycopyrrolate, 0.6 mg. Approximately 1 min after the injection of the reversal drugs, the heart rate began to decrease. The anesthetics were discontinued, and atropine, 1.2 mg IV, was given. However, sinus bradycardia continued to progress for approximately the next 2 min. The heart rate was 42 beats/min, and the arterial blood pressure was 68/40 mm Hg. Heart rate continued to decrease. Epinephrine, 1.0 mg IV, was given rapidly, and external cardiac massage was initiated. The response to these measures was prompt: blood pressure and heart rate increased to 210/90 mm Hg and 132 beats/min, respectively. Blood loss was estimated at 250 ml.

In the recovery room, the patient was fully awake. Vital signs were stable. The endotracheal tube was removed. The patient was observed in the intensive care unit for the next 8 hr. Serial ECGs showed no changes from the preoperative tracing. Plasma levels of cardiac enzymes were not elevated. The patient was discharged from the hospital 11 days after the last operation. The stump wound was healing well.

Two weeks after the discharge, the patient's cardiovascular reflexes, i.e., changes in heart rate during

deep breathing at the rate of 6/min and with the Valsalva maneuver, as well as the blood pressure response to sustained handgrip, were measured during one of his postoperative followup visits. An electrocardiographic tracing was recorded continuously during the tests. All tests were repeated three times, and the mean values were used as the results. The resting heart rate was 102 beats/min. Beat-to-beat variation during deep breathing was 0.6, and the Valsalva ratio 1.03. The diastolic pressure increased 11 mm Hg during the handgrip test. Changes in heart rate and blood pressure in response to standing could not be evaluated because the patient was an amputee.

Discussion

Autonomic neuropathy was considered to be a late complication of diabetes until recently. However, studies of the cardiovascular system, the urinary bladder, the gastrointestinal tract, and the iris have shown that autonomic nerve function is abnormal early in the course of the disease before the appearance of clinical signs and symptoms of autonomic neuropathy (5-8). Abnormal cardiovascular nerve function often coexists with peripheral neuropathy, and evidence exists that peripheral and autonomic neuropathy may develop in a parallel manner (9,10).

Five noninvasive tests are currently used to assess cardiovascular autonomic function. These tests measure heart rate responses to deep breathing, standing and the Valsalva maneuver, and blood pressure responses to standing up and to sustained hand grip (isometric exercise). Sinus arrhythmia, the initial tachycardia of the biphasic heart rate response to standing considered to be due to vagal withdrawal, and the post-Valsalva bradycardia are all abolished with atropine but not with β -adrenergic antagonists, suggesting that these responses are under vagal control (11-13). In normal subjects, reflex vasoconstriction and an increase in heart rate tend to restore blood pressure and cardiac output on standing from the supine position. There is a concomitant increase in the plasma norepinephrine concentration. A recent study has shown that the increases, after standing, in total peripheral vascular resistance, splanchnic vascular resistance, and subcutaneous vascular resistance as well as plasma norepinephrine response were all significantly less in the diabetic with orthostatic hypotension (14). In this study, blood volume and the decrease in cardiac output and plasma volume after standing were similar in the diabetics with and without orthostatic hypotension. These findings together suggest that diabetic orthostatic hypotension is primarily due to a lack of vasoconstriction secondary to

sympathetic nerve dysfunction. The increase in blood pressure during sustained isometric muscular exercises, e.g., handgrip, is due to increase in peripheral vascular resistance and cardiac output. This response is significantly attenuated by phentolamine, indicating that it is mediated by the sympathetic nervous system (15).

Heart rate and blood pressure responses to these maneuvers are reproducible in normal subjects but often decreased in long-term diabetics. Recently, Ewing et al. reported their 10-yr experience with these five tests in normal subjects and diabetics (1). They considered each of the following abnormal: a beat-to-beat variation <10 beats/min (the difference between maximal and minimal heart rate during deep breathing at the rate of 6 breaths/min); a 30:15 ratio <1.03 (the ratio of R-R intervals at beats 15 and 30 after standing); the Valsalva ratio <1.20 (the ratio of the longest R-R interval after the maneuver to the shortest R-R interval during the maneuver blowing against a pressure of 40 mm Hg for 15 sec); a decrease in the systolic pressure on standing >30 mm Hg; or an increase in the diastolic pressure during sustained handgrip at 30% of the maximal voluntary contraction <15 mm Hg. These tests are not specific for autonomic nerve function. An abnormality anywhere along the reflex arc, i.e., a sensor, afferent nerve, reflex center, efferent nerve, and effector organ, can alter the effector organ response. However, diabetics with clinical signs of autonomic neuropathy invariably have abnormal results in one or more of the above tests, and the results of different tests of parasympathetic nerve function correlate closely with each other. Thus abnormal results in diabetics have been considered indicative of autonomic neuropathy (16).

Studies of diabetics using these tests have shown that the heart rate responses to deep breathing and standing are more prevalent than those to the Valsalva maneuver and that parasympathetic abnormality is more prevalent than sympathetic abnormality (1). Sinus arrhythmia can be blocked with a lower dose of atropine than can the Valsalva response (17). Thus the heart rate response to deep breathing appears to be a more sensitive test for cardiac vagal impairment, and the Valsalva ratio may be useful in the detection of more severe impairment. Diabetics with abnormal cardiac vagal function may have normal sympathetic function, but diabetics with abnormal sympathetic function invariably have abnormal vagal function. However, plasma catecholamine responses to standing, exercise, an hypoglycemia in diabetics with normal blood pressure responses to standing and isometric muscular exercise, i.e., handgrip, are blunted and correlate with abnormal cardiac

vagal function (16). Thus sympathetic, parasympathetic, and somatic neuropathy may develop in a parallel manner in diabetic patients.

Late complications of diabetes mellitus, i.e., proliferative retinopathy, chronic renal insufficiency, peripheral vascular disease, and peripheral somatic neuropathy were present in our patient. None of the complications were incapacitating, and the patient had led an active life until the onset of the present illness, which resulted in an above knee amputation. There were no symptoms suggestive of autonomic neuropathy, e.g., postural hypotension, sweating disturbances, gastric symptoms, diarrhea, or urinary bladder or sexual dysfunctions. However, the resting heart rate was elevated persistently in the range of 90 to 106 beats/min, and the results of a postoperative study of cardiovascular reflexes were consistent with severe damage of cardiac parasympathetic pathways. There was essentially no change in heart rate during either deep breathing or the Valsalva maneuver. The diastolic blood pressure increase in response to sustained handgrip was borderline.

It is difficult to explain why the episode of bradycardia that this patient suffered did not respond to an additional dose of anticholinergic (atropine) after glycopyrrolate. Bradycardia can occur after reversal of muscle relaxants with neostigmine and anticholinergic in the usual clinical doses, but the progression of bradycardia almost to the point of sinus arrest is rare. The bradycardia usually responds to anticholinergics. A completely denervated heart, i.e., a transplanted heart, beats at its intrinsic rate, neither atropine, glycopyrrolate nor neostigmine having any effect on heart rate (18-20). The development of bradycardia, therefore, suggests that some degree of acetylcholine-mediated nerve impulse transmission to the receptor in the heart, e.g., S-A node, was present in our patient despite evidence consistent with severe damage to the cardiac vagus nerve. Vital signs in our patient had been stable with 0.25% isoflurane and 50% nitrous oxide during the entire anesthetic. Oxygenation and ventilation were optimal. Blood loss was minimal. Thus anesthetic-induced myocardial depression, hypoxia, or significant blood volume deficit do not appear to explain the episode. Myocardial infarction was ruled out by postoperative serial enzymes and electrocardiograms.

Denervated organs often develop hypersensitivity to the synaptic transmitter substances. Hypersensitivity to adrenergic stimulation occurs after chronic β -adrenergic blockade (21). Unstable angina or myocardial infarction can develop precipitously after abrupt propranolol withdrawal in patients with coronary artery disease (22,23). Prolonged stimulation, on the

other hand, of β -adrenergic receptors with β -agonist, e.g., isoproterenol, results in inactivation or a functional reduction in the number of receptors (21). Denervated muscles develop hypersensitivity to succinylcholine. The receptor area of denervated muscle enlarges progressively until the entire surface membrane of the muscle fiber develops sensitivity to chemical depolarization (24). Such muscles, after administration of succinylcholine, contract more forcefully, remain depolarized longer, and release more potassium than normal muscles (25). There are also reports to suggest that cardiac denervation hypersensitivity may develop in diabetics with autonomic neuropathy. When challenged by hypoglycemia, the heart rate increase in diabetics with autonomic neuropathy was greater than normal subjects for the same magnitude of increase in plasma epinephrine (26). Christensen showed an increased sensitivity to infusions of catecholamines in diabetics with autonomic neuropathy (27).

An appealing assumption in this patient would be that hypersensitivity of the vagal postsynaptic receptor secondary to cardiac vagal neuropathy was responsible for the episode of bradycardia and, therefore, the dose of anticholinergic to block the cardiac muscarinic effect was greatly increased. This assumption would explain the apparent failure of an additional dose of anticholinergic to prevent the progression of bradycardia. Blood pressure responses to standing and isometric muscular exercise depend on changes in total vascular resistance. Such tests are unlikely to be sensitive enough to detect a regional sympathetic impairment such as cardiac sympathetic nerves. A borderline result in the handgrip test suggests that an overall sympathetic nerve function may have been impaired substantially. Impaired cardiac sympathetic nerves as well as generalized sympathetic neuropathy could also have contributed to the bradycardia.

The severity of autonomic neuropathy usually progresses with time. Once autonomic neuropathy develops, the prognosis is poor and the mortality rate is in excess of 50% over a 5-yr period (28,29). Many of these deaths were "unexpected" and were considered to be due to an abnormality of cardiovascular innervation. Diabetics with autonomic neuropathy should be observed carefully for abnormal circulatory responses to the drugs that affect the autonomic nervous system and the unexpected cardiorespiratory depression during the perioperative period. In consideration of the frequent coexistence of peripheral and autonomic neuropathy, we feel it advisable to perform cardiac autonomic nerve function tests in those

diabetics with peripheral neuropathy and/or clinical symptoms of autonomic neuropathy.

References

1. Ewing DJ, Martyn CN, Young RJ, Clarke BF. The value of cardiovascular autonomic function tests: 10 years experience in diabetes. *Diabetes Care* 1985;8:491-8.
2. Faerman I, Faccio E, Milei J, Nunez R, Jadzinsky M, Fox D, Rappaport M. Autonomic neuropathy and painless myocardial infarction in diabetic patients. *Diabetes* 1977;26:1147-58.
3. Page MMB, Watkins PJ. Cardiorespiratory arrest and diabetic autonomic neuropathy. *Lancet* 1978;ii:14-6.
4. Ciccirelli LL, Ford CM, Tsueda K. Autonomic neuropathy in a diabetic patient with renal failure. *Anesthesiology* 1986;64:283-7.
5. Pfeifer MA, Cook D, Brodsky J, Tice D, Reenan A, Swedine S, Halter JB, Porte D Jr. Quantitative evaluation of cardiac parasympathetic activity in normal and diabetic man. *Diabetes* 1982;31:339-45.
6. Buck AC, McRae CU, Reed PI (Chisholm GD). Abstract 22. Abnormal detrusor function in asymptomatic diabetes. *Br J Surg* 1973;60:310.
7. Mandelstam P, Siegel CI, Lieber A, Siegel M. The swallowing disorder in patients with diabetic neuropathy-gastroenteropathy. *Gastroenterology* 1969;56:1-12.
8. Pfeifer MA, Cook D, Brodsky J, Tice D, Reenan A, Parrish D, Halter JB, Porte D Jr. Quantitative evaluation of sympathetic and parasympathetic control of iris function. *Diabetes Care* 1982;5:518-28.
9. Ewing DJ, Campbell IW, Burt AA, Clarke BF. Vascular reflexes in diabetic autonomic neuropathy. *Lancet* 1973;ii:1354-6.
10. Tackmann W, Kaeser HE, Berger W, Rüeger AN, Violier E. Autonomic disturbances in relation to sensorimotor peripheral neuropathy in diabetes mellitus. *J Neurol* 1981;224:273-81.
11. Wheeler T, Watkins PJ. Defective innervation of heart in diabetic autonomic neuropathy. *Br Med J* 1975;2:15-7.
12. Spodick DH, Meyer MB, Quarry-Pigot VM. Effect of beta-adrenergic blockade on beat-to-beat response to the Valsalva manoeuvre. *Br Heart J* 1974;36:1082-6.
13. Ewing DJ, Hume L, Campbell IW, Murray A, Neilson JMM, Clarke BF. Autonomic mechanisms in the initial heart rate response to standing. *J Appl Physiol* 1980;49:809-14.
14. Hilsted J, Parving HH, Christensen NJ, Benn J, Galbo H. Hemodynamics in diabetic orthostatic hypotension. *J Clin Invest* 1981;68:1427-34.
15. Lind AR, Taylor SH, Humphreys PW, Kennelly BM, Donald KW. The circulatory effects of sustained voluntary muscle contraction. *Clin Sci* 1964;27:229-44.
16. Hilsted J. Pathophysiology in diabetic autonomic neuropathy: cardiovascular, hormonal, and metabolic studies. *NY State J Med* 1983;82:892-903.
17. Pfeifer MA, Weinberg CR, Cook D, Halter J, Porte D Jr. Sensitivity of R-R variation and the Valsalva ratio in the assessment of diabetic autonomic neuropathy. *Clin Res* 1983;31(2):394A.
18. Shaver JA, Leon DF, Gray S, Leonard JJ, Bahnson HT. Hemodynamic observations after cardiac transplantation. *N Engl J Med* 1969;281:822-7.
19. Kanter SF, Samuels SI. Anesthesia for major operations on patients who have transplanted hearts, a review of 29 cases. *Anesthesiology* 1977;46:56-8.
20. Eisenkraft JB, Dimich I, Sachdev VP. Anesthesia for major non-

- cardiac surgery in a patient with a transplanted heart. *Mount Sinai J Med* 1981;48:116-20.
21. Bondoulas H, Lewis KP, Kates RE, Dalamangas G. Hypersensitivity to adrenergic stimulation after propranolol withdrawal in normal subjects. *Ann Intern Med* 1977;87:433-6.
 22. Alderman EL, Coltart J, Wettach GE, Harrison DC. Coronary artery syndromes after sudden propranolol withdrawal. *Ann Intern Med* 1974;81:625-7.
 23. Harrison DC, Alderman EL. Discontinuation of propranolol therapy. Cause of rebound angina pectoris and acute coronary events. *Chest* 1976;69:1-2.
 24. Thesleff S. Effects of motor innervation on the chemical sensitivity of skeletal muscle. *Physiol Rev* 1960;40:734-52.
 25. Gronert GA, Theye RA. Pathophysiology of hyperkalemia induced by succinylcholine. *Anesthesiology* 1975;43:89-99.
 26. Hilsted J, Madsbad S, Krarup T, Sestoft L, Christensen NJ, Tromier B, Galbo H. Hormonal, metabolic and cardiovascular responses to hypoglycemia in diabetic autonomic neuropathy. *Diabetes* 1981;30:626-33.
 27. Christensen NJ. Catecholamines and diabetes mellitus. *Diabetologia* 1979;16:211-24.
 28. Ewing DJ, Campbell IW, Clarke BF. Mortality in diabetic autonomic neuropathy. *Lancet* 1976;i:601-3.
 29. Ewing DJ, Campbell IW, Clarke BF. The natural history of diabetic autonomic neuropathy. *Q J Med* 1980;NS49:95-108.

The Successful Treatment of Dural Puncture Headache after Failed Epidural Blood Patch

Curtis L. Baysinger, MD, Emil J. Menk, MD, Edward Harte, MD, and Robert Middaugh, MD

Puncture of the lumbar dura can lead to a severe and often incapacitating headache. A single injection of autologous blood into the epidural space relieves the headache in 90% of the patients so affected, whereas a second blood patch successfully treats the majority of those in whom the first blood patch is ineffective (1). The management of patients in whom the repeat blood patch fails is not clear. We describe the effective treatment of postdural puncture headache in two patients using patient-controlled, continuous, epidural infusion of saline after failed epidural blood patch.

Case 1

A 38-yr-old male with chronic low back pain who had undergone previous lumbar laminectomy was evaluated for paraspinal steroid injections. EMG studies and physical examination of the lower extremity were consistent with chronic nerve root irritation at the left L5-S1 nerve root. The patient was given, on an ambulatory, out-patient basis, two epidural injections of 80 mg methylprednisolone in 1.5% lidocaine at the L4-L5 interspace without relief of symptoms. A subsequent subarachnoid injection of 80 mg of methylprednisolone was performed at the L4-5 interspace using a 22-gauge needle. Approximately 24 hr after the injection, the patient had onset of occipital and bifrontal headache accompanied by nausea and diaphoresis that was relieved by compression of the abdomen and by lying in the supine, horizontal position. Initial therapy of bedrest at home, together with

oral fluids and analgesics failed to relieve his symptoms over the next two days. Four epidural blood patches utilizing 10 cc of autologous blood (1,2) were then performed on an out-patient basis at the L4-5 interspace over the next 18 days with no change in symptoms. His bleeding time was normal. Propranolol, 20 mg, dichloralphenazone, 200 mg, and acetaminophen, 650 mg taken orally four times per day for the next seven days failed to relieve his symptoms. On the 25th day following onset of the headache, the patient was admitted and conservative therapy of strict bedrest in the Trendelenburg position, intravenous fluid hydration with lactated Ringer's solution at 175 ml/hr, and analgesics as needed was initiated. A CT scan of the head showed no abnormality, and a neurological consultation revealed no other pathology. On the 28th day after onset of the headache, an epidural catheter was placed at the L4-5 interspace with the location confirmed by the injection of 2% lidocaine. Normal saline, 50 ml, was injected over 45 min. Pain in the hips, legs, back, and eyes limited the rate of injection. A continuous infusion of saline, regulated by the patient to his tolerance of ocular and back pain, was maintained between 15 and 25 ml/hr. After 26 hr of continuous infusion, the patient was headache-free, and the saline infusion was discontinued. The patient was discharged 24 hr later without symptoms. Direct examination of the retina showed no abnormality, and neurological examination performed three weeks later was unremarkable. Followup at 3 months showed no return of his headache.

Case 2

A 26-yr-old woman underwent attempted epidural anesthesia for cesarean section. Initial placement of the epidural needle at the L3-4 interspace was complicated by dural puncture with the 18-gauge Tuohy needle. A subsequent insertion of an epidural catheter at the L2-3 interspace was successful. A total of 20

The opinions or assertions contained herein are the private views of the authors and are not to be construed as reflecting the views of the Department of the Army or the Department of Defense.

Received from the Anesthesia and Operative Service, Department of Surgery, Brooke Army Medical Center, Fort Sam Houston, Texas. Accepted for publication June 12, 1986.

Address correspondence to Dr. Baysinger, MAJ, MC, Anesthesia and Operative Service, Brooke Army Medical Center, Fort Sam Houston, TX 78234-6200.

ml of 3% 2-chloroprocaine was administered through the catheter, which was then removed after the cesarean delivery. Approximately 12 hr after the dural puncture, the patient had onset of an occipital and bifrontal headache that was relieved by the application of abdominal pressure and by lying in the supine, horizontal position. The patient was treated for 24 hr with intravenous fluids and abdominal binders without significant relief. Epidural blood patches with 10 ml of autologous blood (1,2) were placed 1, 3, and 5 days later at the same interspace as the dural puncture. All blood patches relieved her symptoms for periods up to 12 hr with subsequent return of her postural headache. On the eighth day after onset of the headache, an epidural catheter was placed at the L3-4 interspace and the location confirmed by the injection of 2% lidocaine. Normal saline, 30 ml, was injected over 10 min accompanied by ocular and back pain. A continuous infusion of saline was maintained between 15 and 30 ml/hr for the next 24 hr. Ocular pain limited the upper limit of the rate of infusion. The patient was discharged without a headache 24 hr after discontinuing the infusion. Direct examination of the retina showed no abnormality, and neurological examination performed four weeks later was unremarkable. Followup at 3 months showed no return of her headache.

Discussion

The treatment of postdural puncture headache is directed towards improving the ratio between production of cerebrospinal fluid (CSF) and loss from the subarachnoid space. The most effective methods decrease CSF loss by increasing pressure in the epidural space or stop the loss of CSF by sealing the site of the dural tear (3). The injection of autologous blood into the epidural space increases pressure in that space and forms a clot over the site of the dural tear that prevents CSF loss (4). Although an epidural blood patch is effective in 90% of dural puncture headaches (1,2), reasons for its failure are unclear. In our first patient, abnormal platelet function leading to poor clot formation, a result of chronic antiinflammatory medication use, was ruled out by a normal bleeding time. Chronic scarring in the epidural space after the patient's previous spinal surgery might have prevented spread of the injected blood to the site of the dural tear. In the second patient, clot disruption and reabsorption may have been the mechanism that led to the return of her headache after short periods of relief.

The prophylactic infusion of epidural saline is ef-

fective in reducing the incidence of dural puncture headache in obstetrical patients when started after vaginal or cesarean delivery (5,6). Intermittent boluses of 20-60 ml of saline increase pressure in the epidural space above that in the subarachnoid space for prolonged periods and prevent headache from developing while the dural tear closes by other mechanisms (7). Epidural saline may also help close dural tears by creating dural edema or by encouraging the physical apposition of the edge of the puncture site (3). Although the superiority of blood over saline in relieving headache symptoms has been shown (8), we were able to treat postdural puncture headache by the continuous infusion of saline after the failure of repeated blood patches. This suggests that the continuous infusion of saline may offer an advantage over the previously described methods of intermittent bolus injection of saline.

Patient control of the rate of infusion of saline into the epidural space between set limits may avoid the low back pain, orbital pain, and retinal hemorrhages that can accompany the epidural injection of large volumes of saline (9). In both our patients, orbital pain accompanied the initial bolus of saline and limited the upper rate at which the epidural infusion could be set. Ocular pain probably results from an increase in pressure in the epidural and subarachnoid spaces which is transmitted to the optic nerve (9). Retinal hemorrhages were not seen in either of our patients.

We arbitrarily maintained our epidural infusion for 24 hr, a time that Crawford (7) found successful for prevention of dural puncture headache after inadvertent dural puncture in obstetrical patients. We infused between 15 and 30 ml/hr for 24 hr and used total volumes of 700 ml or less. Crawford infused 1 L of normal saline over a similar time period and successfully prevented headaches in 65% of the patients he treated, a volume somewhat larger than we used.

Using a patient-controlled, continuous, epidural infusion of saline, we successfully treated postdural puncture headache after failed repeated epidural blood patch in two patients. The treatment did not produce neurological abnormality and may avoid the risk of retinal hemorrhage and orbital pain associated with the single bolus injection of large volumes of saline.

References

1. Aboaleish E, De la Vega S, Blendinger I, Tiong-Oen T. Long term followup of epidural blood patch. *Anesth Analg* 1975;54:459-63.
2. Ostheimer GW, Palahniuk RJ, Shnider SM. Epidural blood patch for post lumbar puncture headache. *Anesthesiology* 1974;41:307-8.

Letters to the Editor

RAM Testing in Obstetric Patients

To the Editor:

The article by Van Zundert et al. (*Anesth Analg* 1986;65:333) concluded that in obstetric patients, the rectus abdominus test (RAM test) was more appropriate than the traditional Bromage test for assessing motor function during lumbar epidural anesthesia. Whereas the two tests are alleged to measure motor function of different spinal segmental levels, two aspects of the present study make it difficult to attribute the conflicting results to differences in segmental blockade:

The rectus abdominus muscles are more compromised than hip and leg muscles in the parturient at term.

Bromage compared control with test data in his study; Van Zundert et al. did not.

The authors' assumption that term parturients can easily rise from the supine to the sitting position is no substitute for control data. The absence of such data detracts from the validity of the study's conclusions.

A method such as the RAM test might be valuable in assessing abdominal muscle relaxation except in those patients whose body habitus precludes optimal use of the rectus musculature.

Robert H. Boretsky, MD
*Department of Anesthesiology
Mercy Hospital
Pittsburgh, PA 15219*

In Response:

One should clearly differentiate the RAM-test and the RAM-block. The RAM-test is the difference between two RAM-tests. Usually the first RAM-test measures the power of the abdominal muscles before the block and the second one measures muscle power after the block has settled, or at any other period one is interested in.

In this way, the patient is her own control, and it does not matter if the abdominal muscles in at-term parturients are less or more compromised before anesthesia is administered.

The Bromage-test, on the other hand, is done with the assumption that preblock power is 100%. We never made the assumption that parturients can easily rise from the supine to the sitting position at term. Although it is irrelevant, we provide the further information in our population of the parturients at term:

73% score a preblock RAM-test of 100%
17% score a preblock RAM-test of 80%
8% score a preblock RAM-test of 60%
2% score a preblock RAM-test of 40% or less.

Adrien Van Zundert, MD, PhD
Leo Vaes, MD
Paul Van Der Aa, MD
Agnes Van Der Donck, MD
Herman Meeuwis, MD
*Department of Anesthesiology and Resuscitation
St-Elisabeth Hospital
Turnhout 2300, Belgium*

Succinylcholine-triggered Masseter Spasm in a Patient with Trigeminal Nerve Palsy

To the Editor:

Succinylcholine (Sch)-triggered masseter spasm should always be presumptive of malignant hyperthermia (MH) susceptibility until proven otherwise (1,2). However, before condemning a patient as MH susceptible, we must exclude other causes of masseter spasm, such as myotonia (3). The present case illustrates that denervation of the masseter muscle in a patient with trigeminal nerve palsy can also predispose to Sch-induced masseter spasm.

The patient was a 48-yr-old male, weighing 75 kg, who suffered from a left nasopharyngeal tumor. The patient had a palsy of the left fifth cranial nerve. The left 6th, 7th, 8th, and 9th cranial nerves were also involved. The patient was scheduled for transpalatal biopsy. After preoxygenation with a face mask, anesthesia was induced with intravenous thiopental, 5 mg/kg, plus Sch, 1.5 mg/kg. Generalized muscle fasciculations and apnea followed the injections of Sch. However, it was very difficult to open the mouth of the patient and to perform the laryngoscopy and tracheal intubation. Sch-induced contracture of the denervated jaw muscles was incriminated, and we then injected atracurium, 0.5 mg/kg intravenously, which was followed within 60 sec by complete relaxation of the jaw muscles. The mouth could then be widely opened, and orotracheal intubation was easily performed.

Previous reports have shown that Sch-induced muscle rigidity can occur in denervated limb muscles (4). This has

been attributed to denervation supersensitivity to Sch, which results from extrajunctional spread of the chemoreceptors over the entire muscle membrane. The present report illustrates that a similar response can also occur at the denervated masseter and temporalis muscles, which are innervated by the mandibular division of the trigeminal nerve. Similar to the denervated limb muscles, Sch-triggered rigidity of the denervated jaw muscles can be antagonized by nondepolarizing neuromuscular blocking drugs (5).

Anis Baraka, MD

Musa Muallem, MD

Hoda Karam, MD

Department of Anesthesiology
American University of Beirut
Beirut, Lebanon

References

1. Flewellen EH, Nelson TE. Halothane-succinylcholine induced masseter spasm: indicative of malignant hyperthermia susceptibility? *Anesth Analg* 1984;63:693-7.
2. Fletcher JE, Rosenberg H. In vitro interaction between halothane and succinylcholine in human skeletal muscle: implications for malignant hyperthermia and masseter muscle rigidity. *Anesthesiology* 1985;63:190-4.
3. Baraka A, Haddad C, Afifi A, Baroody M. Control of succinylcholine-induced myotonia by *d*-tubocurarine. *Anesthesiology* 1970;33:669-70.
4. Baraka A. Suxamethonium-induced muscle contracture following traumatic denervation in man. *Br J Anaesth* 1978;50:195-9.
5. Baraka A. Antagonism of succinylcholine-induced contracture of denervated muscles by *d*-tubocurarine. *Anesth Analg* 1981;60:605-7.

Analgesic Potencies of Dezocine and Butorphanol

To the Editor:

I read with interest the recent article by Galloway and Varma (1) on the double-blind comparisons of intravenous dezocine, butorphanol, and placebo for the relief of postoperative pain. This paper may mislead anesthesiologists, as well as other physicians who wish to use these drugs, into thinking that dezocine is a more potent analgesic than butorphanol. The authors compared 5 and 10 mg dezocine to 1 mg butorphanol and to placebo. They found that both active agents afford better pain relief than placebo, which is what one would expect and therefore is nothing new. To compare 5 mg dezocine to 1 mg butorphanol is reasonable: because 1 mg butorphanol is equal to 5 mg of morphine sulfate, and because 10 mg dezocine is as effective in analgesic relief as 10 mg morphine sulfate, then 5 mg dezocine would have equianalgesic effectiveness to 5 mg morphine sulfate. To compare 10 mg dezocine to 1 mg butorphanol is, however, not reasonable because the drugs are not equally potent mg for mg. Because 10 mg dezocine is as effective an analgesic as 10 mg morphine sulfate, as stated by the authors, 10 mg dezocine should have been compared to 2 mg butorphanol, because 2 mg butorphanol is equal to 10 mg morphine sulfate (2). Had they used 2 mg butorphanol, they might have found that this latter dose may have af-

forded better and more prolonged (3) pain relief than 10 mg dezocine.

Maurice Lippman, MD
Department of Anesthesiology
UCLA School of Medicine
Harbor/UCLA Medical Center
Torrance, CA 90509

References

1. Galloway FM, Varma S. Double-blind comparison of intravenous doses of dezocine, butorphanol, and placebo for relief of postoperative pain. *Anesth Analg* 1986;65:283-7.
2. Lippmann M, Mok MS, Steen SN, Caruso FS. Butorphanol and morphine: a double-blind multiple intramuscular dose comparative safety and efficacy study in patients with postoperative pain. *Curr Ther Res* 1977;21:427-34.
3. Lippmann M, Mok MS, Steen SN. Analgesic onset time of intravenous butorphanol in postsurgical patients: a placebo-controlled study. *Curr Ther Res* 1977;22:276-83.

In Response:

Dezocine is an investigational drug, and consequently the relation between the dose of dezocine and its efficacy and safety has not yet been fully established. Therefore, although one might logically assume by extrapolating from the potencies of both butorphanol and dezocine relative to morphine sulfate that 1 mg butorphanol would be equianalgesic to 5 mg dezocine (1), testing this assumption in a clinical situation certainly did not constitute a "flawed" study design. We compared the recommended initial dose of intravenously administered butorphanol (2) with two doses of the investigational analgesic and found 5 mg dezocine and 1 mg butorphanol had comparable analgesic effects, whereas 10 mg dezocine was superior in efficacy to 1 mg butorphanol, as might be expected on the basis of potency assumptions. We found no statistically significant difference, however, between 1 mg butorphanol and 10 mg dezocine in the incidence of side effects possibly related to these two drugs. Despite this fact, we are not claiming that dezocine is better than butorphanol; simply that 10 mg dezocine was more effective than 1 mg butorphanol in this study. Furthermore, Dr. Lippman's speculation that 2 mg butorphanol may have afforded "better and more prolonged pain relief" than 10 mg dezocine is not substantiated by results of his study (3) in which he found that 2 mg butorphanol was "analgesically equivalent" to 10 mg morphine administered intramuscularly.

Frederick M. Galloway, MD
Department of Anesthesiology
Denver General Hospital
Denver, CO 80204

References

1. Galloway FM, Varma S. Double-blind comparison of intravenous doses of dezocine, butorphanol, and placebo for relief of postoperative pain. *Anesth Analg* 1986;65:283-7.
2. 1986 Physicians' Desk Reference®. Oradell, New Jersey: Medical Economics Company, Inc., 1986:713.
3. Lippmann M, Mok MS, Steen SN. Butorphanol and morphine: a double-blind multiple intramuscular dose comparative safety and efficacy study in patients with postoperative pain. *Curr Ther Res* 1977;21:427-34.

Figure 1. Disposable tubing attached to the output port of the Concha Therm III humidifier melted as the water bath overheated.



Disposable Circuit Tubing Melted by Heated Humidifier

To the Editor:

Potential problems associated with the use of heated humidifiers include excessive condensation, large decreases in pressure across the humidifier chamber, cross infection, and respiratory tract burns from overheated humidified gases. We recently added another problem to this list when we observed melting of disposable circuit tubing (Dryden Corporation) attached to a Concha Therm III humidifier (Fig. 1).

Heated humidifiers with the primary control disabled are capable of producing water temperatures (62–139°C) that can severely burn the airway (1). To help prevent this complication, it has been suggested that a temperature monitor-controller be used in the circuit at the site of connection with the patient's airway. However, with low flow rates, use of a temperature monitor-controller with the Concha Therm III humidifier does not eliminate the possibility of overheating of the water bath. If overheating develops, melting of disposable circuit tubing attached to the output port of the humidifier may occur.

Investigation of this problem with a temperature monitor at the unconnected airway end of the circuit revealed that melting of disposable tubing attached to the humidifier occurred within 15 min of activating the humidifier when no flow of gas passed through the circuit. If a flow of 750 ml of gas were delivered through the circuit, melting occurred at approximately 22 min as a temperature of 75°C developed at the output port of the humidifier. No melting of the tubing occurred if flows were greater than 1000 ml/min. However, even though disposable tubing did not melt at

gas flows of 1000 ml/min or greater, the case surrounding the humidifier became hot enough to cause a burn on contact, and the disposable tubing at the point of connection to the humidifier was easily distorted and dislodged with a slight force.

The manufacturer of the Concha Therm III, Respiratory Care, Inc., recommends not activating the humidifier before turning on a high gas flow. This advice is imperative if the hazards of using disposable tubing with this humidifier are to be avoided.

David H. Sprague, MD
Gerald A. Maccioli, MD
*Department of Anesthesiology
University of North Carolina
Chapel Hill, North Carolina 27514*

Reference

1. Staewen WS. Temperature control of heated humidifiers. *Med Instrum* 1982;16:55-6.

Laboratory False-positive Hyperkalemia in a Patient with Cold Agglutinins

To the Editor:

We recently encountered a patient in whom severe hyperkalemia proved to be an artifact of interaction between the patient's underlying condition and the handling of a laboratory specimen.

A 77-yr-old man with known cold agglutinins underwent uncomplicated nitrous oxide/enflurane anesthesia for bilateral femoral-popliteal bypass grafts. Immediately postop-

eratively, an arterial blood specimen was sent on ice to the laboratory for measurement of gas tensions but was clotted. A second iced sample was also clotted but tested and revealed a potassium (K^+) of 7.5 mEq/L. The electrocardiogram was unchanged from baseline. We subsequently drew two samples, keeping one at room temperature and placing the second on ice. The room temperature sample had a K^+ of 3.8 mEq/L; the iced sample K^+ was 6.1 mEq/L. Both samples were "clotted," which actually represented agglutination, but hemolysis sufficient to increase plasma levels of potassium occurred only in the iced specimen. Because potassium levels are measured in our laboratory using whole blood, hemolysis would be noted only if a hematocrit is requested and the sample centrifuged.

On careful clinical evaluation, the patient had no other apparent reason to be hyperkalemic to the extent noted, nor was he treated for this symptom. Cold agglutinins should be added to the list of causes of laboratory false-positive hyperkalemia. This case reaffirms the importance of interpreting laboratory abnormalities in the complete clinical context.

James R. Hlavacek, MD
Department of Anesthesiology
St. Elizabeth's Hospital
Brighton, MA 02135

Richard Restifo
David Stone, MD
David Cullen, MD
Harvard Medical School
Massachusetts General Hospital
Boston, MA 02114

Reference

1. Stein JH (ed.). Internal medicine. Boston: Little Brown, 1983:731-3.

Hypertensive Response to Dinoprost under Anesthesia

To the Editor:

I would like to draw readers' attention to a problem with the oxytocic dinoprost tromethamine (Prostin $F_2\alpha$ ®).

Case: A 24-yr-old woman was scheduled for uterine dilation and curettage 10 days postpartum. Six hours prior to arrival in the operating room, she received 2 mg methylergonovine (Methergine®) IM. She had no allergies and was taking no medications. After 1000 ml of lactated Ringer's solution, and 5 min of preoxygenation, anesthesia was induced with 250 mg thiopental, followed by 100 mg succinylcholine. The trachea was intubated with a 7.5 cuffed endotracheal tube. Anesthesia was maintained with nitrous oxide 60%, oxygen 40%, and isoflurane (0.5% inspired). Monitors included a precordial stethoscope, an ECG, a non-invasive blood pressure monitor, a pulse oximeter and an end tidal CO_2 monitor. Because of uterine atony, the surgeon injected 2.5 mg of dinoprost tromethamine into the uterine muscle. Within seconds of the injection, the pa-

tient's heart rate increased to 175 beats/min and her blood pressure went from 115/72 torr to 220/135 torr. There were no changes in SpO_2 or end tidal CO_2 . The isoflurane was increased with little change in vital signs. Her heart rate and blood pressure gradually decreased over the next few minutes to within normal limits. She awoke with no difficulties.

Prostin $F_2\alpha$ is a salt of the naturally occurring prostaglandin $F_2\alpha$ (PGF $_2\alpha$) and not only is an active stimulator of uterine contraction but a potent chronoscope and peripheral alpha-adrenergic (1) agonist. Extreme caution must be exercised when this agent is injected into a vascular muscle such as a postpartum uterus.

James F. Mayhew, MD
Department of Anesthesiology
Oral Roberts University
Tulsa, OK 74170-7070

Reference

1. Kadowitz PJ, Joiner PD, Greenberg S, et al. Comparison of the effects of prostaglandins A, E, F and B on the canine pulmonary vascular bed. In: Samuelsson B, Paoletti R, eds. Advances in prostaglandin and thromboxane research. New York: Raven Press, 1976:403-15.

Monitoring Inspired Oxygen Concentrations in Nonrebreathing Systems

To the Editor:

Many anesthesiologists prefer using nonrebreathing systems for the induction and/or maintenance of anesthesia. This is especially true in infants and young children. Although it is common for anesthesia personnel to monitor inspired oxygen concentrations while using circle delivery systems, I am not aware of any commercially available device that would allow this same monitoring while using the nonrebreathing system.

I have fabricated a simple device using commonly available and inexpensive components to accomplish this need. The necessary components including parts numbers include the following:

1. An oxygen sensor manifold. This is available from several sources. The one shown in Figure 1 is from Ohmeda/Teledyne (#220-1065-300).
2. Two mask intubation adapters, each 22 mm/15 mm. Those shown in Figure 1 are Bird adapters (#999-1233).
3. One plastic 22-mm coupling (Bird #423).
4. Three 7-mm endotracheal tube adapters along with a short section of a 7-mm endotracheal tube.

The items are connected together to form the completed monitoring assembly as shown in Figure 1.

After the oxygen sensor is seated in the manifold, the entire device is placed between the anesthesia machine's fresh gas outflow and the gas delivery hose of the nonrebreathing system as shown in Figure 2.

Figure 1. The components of the monitoring assembly.

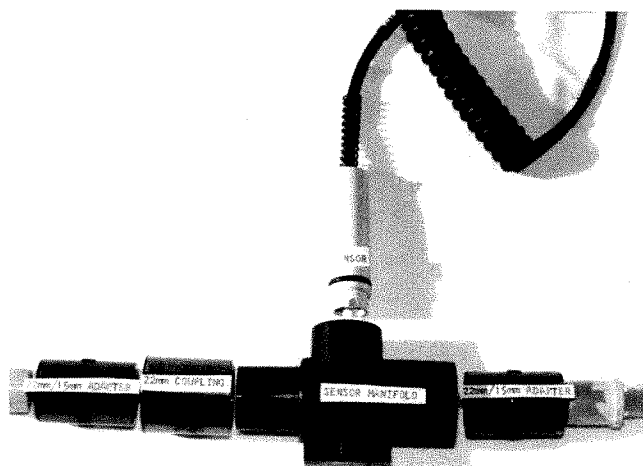
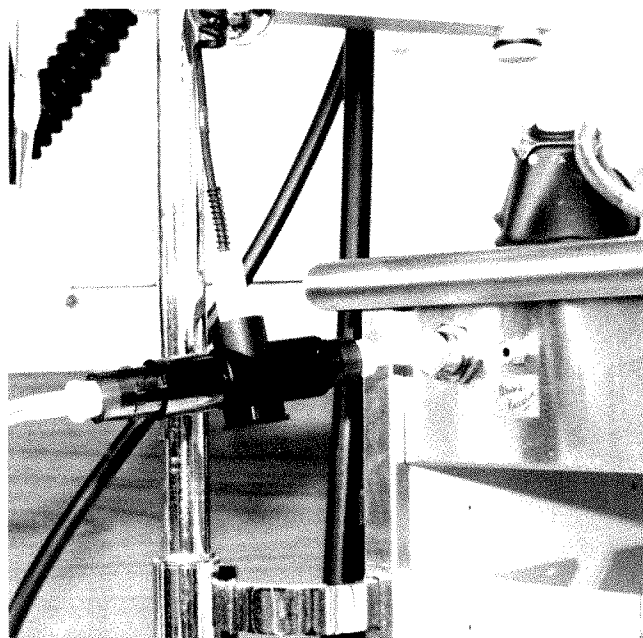


Figure 2. The placement of the device in the circuit.



All of the items I used to fabricate this device should be available through most respiratory care departments. The oxygen sensor manifolds should be available through service representatives of companies that sell oxygen monitors. I have used this device for several years without difficulty. During that time I have not detected any adverse or untoward events associated with its use.

The greatest potential hazard, caused by the increased number of linkages in the gas delivery hose, is disconnection of the fresh gas inflow line. Prudent vigilance will prevent this or other problems with the use of this device.

Donald W. Claeys, MD
McKenzie Anesthesia Group
Springfield, OR 97405

Cushing's Contributions to Anesthesia: Two Comments

To the Editor:

As a former Chief of Anesthesia at the Peter Bent Brigham Hospital where Harvey W. Cushing was its first Surgeon in Chief, I read with more than usual interest the special article, *Harvey Cushing: His Contribution to Anesthesia*, written by Hirsch and Smith (1). As bibliographic research rarely extends beyond a generation these days, they have overlooked an almost identical article written by Shephard in 1965 (2) and further illumination of Cushing's contributions as provided by Moore in 1969 (3). Further, as Cushing's

major accomplishment may have been his recognition of the need for physician-anesthesia, Hirsch and Smith might have consulted the undersigned's brief biography of Walter M. Boothby, Cushing's anesthetist, published in 1967 (4).

Cushing's contributions to anesthesia were even more fundamental to the practice of anesthesia than suggested by Hirsch and Smith. Shephard noted that Cushing was the first to advocate employment of a precordial stethoscope in his Baltimore clinic (5). John Fulton, Cushing's biographer, considered this to be, "one of Cushing's most significant contributions to American surgery (sic)." Moore recalled that Cushing was the first to employ positive pressure ventilation via tracheostomy to treat experimental pneumothorax in the dog. And Cushing, recognizing the value of Ringer's solution in fluid therapy, devised a more elaborate electrolyte solution which was administered as Cushing's solution until recent years at the Brigham (6).

Finally, Cushing was not only a Pulitzer prize-winning biographer (7) but a consummate water colorist and medical illustrator as well.

Leroy D. Vandam, MD
Department of Anesthesiology
Brigham and Women's Hospital
Boston, Massachusetts

References

1. Hirsch NP, Smith GB. Harvey Cushing: his contribution to anesthesia. *Anesth Analg* 1986;65:288-93.
2. Shephard DAE. Harvey Cushing and anaesthesia. *Can Anaes Soc J* 1965;12:832-42.
3. Moore FD. Harvey Cushing: general surgeon, biologist, professor. *J Neurosurg* 1969;31:262-70.
4. Vandam LD, Walter M. Boothby, M.D.—the wellsprings of anesthesiology. *N Engl J Med* 1967;276:558-63.
5. Cushing HW. Some principles of cerebral surgery. *JAMA* 1909;52:184-92.
6. Cushing H. Concerning the poisonous effect of pure sodium chloride solutions upon the nerve muscle preparation. *Am J Physiol* 1901;6:77-90.
7. Cushing HW. *The life of Sir William Osler*. Oxford: Clarendon Press, 1925.

To the Editor:

The plea of Hirsch and Smith that Harvey Cushing's contribution to anesthesia should not be forgotten (1) will, I am sure, not go unheeded. Hirsch and Smith have done well to remind us of Cushing's role in ether charts, sphygmomanometry, and the term "regional anesthesia." However, in the interest of that degree of accuracy demanded of a paper published under the rubric of a Special Article, I feel compelled to make three comments on an otherwise informative account.

First, Hirsch and Smith correctly emphasize the contribution that Cushing made by developing, with Ernest Codman, the ether charts that constituted the prototype of anesthesia records. But, while a certain bias on the part of anyone from Yale in favor of Cushing is understandable, these authors failed to stress two small aspects of the story. As Cushing himself made clear (2), it was, in fact, Codman who used an ether chart first. Beecher emphasized Codman's priority (albeit quoting Codman himself on this) and,

in addition, reported that the idea of ether charts actually originated not with either Codman or Cushing but with Codman's chief, F.B. Harrington (3).

Second, Hirsch and Smith surprisingly do not discuss a further aspect of Cushing's interest in intraoperative monitoring. While Cushing's best-known contribution to monitoring was the introduction of the Riva-Rocci sphygmomanometer into North American operating rooms, Cushing also attached great importance to precordial auscultation during surgery. Hirsch and Smith note that Cushing recognized the importance of employing a physician full-time as anesthesiologist—in the person of Dr. S. Griffith Davis—but they would have done well to quote Cushing more fully on the anesthesiologist's contribution here. In a paper published in 1909 he stressed the value of precordial auscultation:

With a patient in . . . [the] prone position it is difficult for the anesthetist to gauge fully the variation in cardiac action, and . . . Dr. Davis has employed . . . a simple device, so satisfactory that we wonder why it has not long since come into general use—namely, the *continuous auscultation of cardiac and respiratory rhythm during the entire course of anesthesia* (4).

Davis used a "phonendoscope" attached to the chest over the heart and connected by a tube to the anesthesiologist's ear. Cushing continued:

Uninterrupted information of the patient's condition is thus given, and the anesthetist need not disengage a hand for the occasional palpation of the pulse, which is all that he is usually expected to do. On several occasions, by the prompt appreciation of change in heart beat or respiration thus acquired, it has been possible to avert what otherwise might have been surgical disasters, owing to the immediate warning which led to the cessation of certain disturbing manipulations.

Cushing also described how the practice of precordial auscultatory monitoring arose: in his Hunterian Laboratory he and his students developed the practice, while experimentally producing valvular lesions in the dog, of auscultating the heart. (The paper in which the production of these lesions was described is, in itself, an example of Cushing's prescience relating to cardiac surgery, for Cushing used the phrase "future surgery of the cardiac valves" in the title of this 1908 paper.) (5)

Finally, may I add a further reference to this discussion on Cushing and anesthesia? A paper published over 20 years ago (6) amplifies the points I have made here and affirms my support for the plea that Drs. Hirsch and Smith make that Cushing's contributions to anesthesia should indeed not be forgotten. (6)

David A.E. Shephard, MB, FRCP

Department of Anaesthesia
College of Medicine
University of Saskatchewan
Plains Health Centre
Regina, Saskatchewan S4S 5W9
Canada

References

1. Hirsch NP, Smith GB. Harvey Cushing: his contribution to anesthesia. *Anesth Analg* 1986;65:288-93.
2. Cushing HW. On the avoidance of shock in major amputations by cocaineization of large nerve-trunks preliminary to their division with observations on blood-pressure changes in surgical cases. *Ann Surg* 1902;36:321-45.
3. Beecher HK. The first anesthesia records (Codman, Cushing). *Surg Gynecol Obstet* 1940;71:689-93.
4. Cushing HW. Some principles of cerebral surgery. *JAMA* 1909;52:184-92.
5. Cushing HW. Experimental and clinical notes on chronic valvular lesions in the dog and their possible relation to a future surgery of the cardiac valves. *J Med Res* 1908;12:471-86.
6. Shephard DAE. Harvey Cushing and Anaesthesia. *Can Anaesth Soc J* 1965;12:431-42.

In Response:

We thank Dr. Vandam for giving us the opportunity to clarify certain points concerning Harvey Cushing's role in the history of anesthesia.

First, Dr. Vandam claims that "Moore recalled that Cushing was the first to employ positive pressure ventilation via tracheostomy to treat experimental pneumothorax in the dog." However, Cushing never claimed to have been the originator of an idea that had been employed by Vesalius in 1555 (1), Hooke in 1667 (2), and Matas in 1899 (3). In fact, Cushing gave due credit to the fact that direct inflation of the lungs by opening the trachea, was "commonly used in a physiologic laboratory. . . ." (4). Further, the French surgeons Tuffier and Hallion were performing thoracotomies on patients maintained with positive pressure ventilation (5,6) at least a decade prior to Cushing's article (4).

Second, Cushing's role in the production of the elaborate electrolyte solution, which bears his name, is unclear. It is certain that in 1901, continuing from the pioneering work of Sydney Ringer (7), Cushing investigated the effects of similar solutions given intravenously and intraarterially on the contractile state of frog muscle (8). However, on February 9, 1935, Elliot Cutler, Cushing's successor in the chair of surgery at Harvard, wrote to Cushing after problems associated with intravenous solutions given to patients. His letter stated:

The curious part of this whole story is that no one has really worked upon this matter seriously since your publication . . . Now Carl Walter, the Harvey Cushing fellow, has unearthed your publications dealing with the poisonous effect of saline on nerve and muscle tissue and with your approval I am going back to utilise your fluid. (9)

Two days later, Cushing replied:

As a matter of fact, in the early years of the hospital, being uneasy about the sterility of the fluids, I ceased using them for intravenous therapy. I am glad you

have put someone to work on the subject, for it is high time it was reviewed . . . I published a brief report based merely on muscle fatiguability to electrical stimulus in the American Journal of Physiology . . . Later on, for Cohen's System of Physiological Therapeutics (1902) I wrote a pot-boiler (Chapter V) on saline irrigations and infusions . . . You must remember this was ten years before the opening of the Brigham Hospital, and what formulae may have been introduced there I do not know . . . However, as I have said, it is just as well to forget about all these papers and for someone to begin again from the bottom. Just how the high potassium content got into the present Brigham formula I can't imagine. (9)

It is therefore likely that "Cushing's Solution" was given its eponymous title out of respect for Cushing rather than because he was responsible for its adoption into clinical practice. Moreover, it is interesting that other variations of Ringer's solution, such as Darrow's and Hartmann's, were adopted internationally and are still readily available, whereas Cushing's solution clearly enjoyed a limited popularity based in Boston and had a clinical life span of less than 35 years.

Third, regarding Cushing's employment of a precordial stethoscope, Vandam writes that "John Fulton, Cushing's biographer, considered this to be 'one of Cushing's most significant contributions to American Surgery' ". In quoting others, it is important to be accurate and it should therefore be noted that what Fulton actually wrote was "It has been said that one of Cushing's most significant contributions to American Surgery lay in the establishment of the 'Old Hunterian', an experimental surgical laboratory . . ." (10).

Dr. Vandam further suggests that his own article regarding Walter Boothby (11) might have contributed to our own work. However, we feel that we have indeed attached sufficient importance to Cushing's recognition of the need for safe anesthesia and a physician expert in its art. He is, however, correct in indicating that we were unaware of the articles by Shephard (12) and Moore (13), although not totally unaware of their content. The most worrying aspect of this oversight is that, despite two thorough computer searches (including one relating specifically to historical aspects of medicine), access to a large amount of Cushing artifacts, much of Fulton's material on which Cushing's biography was based and a considerable amount of literature from the History of Medicine Library at Yale, we were unable to uncover any previous article relating to Cushing and anesthesia. It is, perhaps, a reflection on the poor manner in which medical articles were catalogued until recently, that, in the last few days, we have fortuitously unearthed an article by Fulton himself that relates to Cushing's involvement in anesthesia (14). This document predates even Shephard's by 19 years!

Dr. Shephard's article (12), however, remains an excellent and most eloquent review of Cushing's interest in anesthesia, and we wholeheartedly congratulate Dr. Shephard on that work. He is correct in reminding us of the involvement of Harrington and Codman in the history of the 'ether charts,' and we must apologize for any apparent bias on behalf of Cushing, as it was unintentional. However, it is

an indication of Cushing's tidy, methodical, and meticulous mind that he was responsible for expanding on their ideas and further improving on the recording of data available during anaesthesia.

With regard to Cushing's advocacy of precordial auscultation, we must agree with Dr. Shephard that this would have been a topic worthy of inclusion in our report. Exactly how much credit is due to Cushing and how much to S. Griffith Davis is difficult to ascertain from the original articles; however, we must accept that Cushing was certainly responsible for publicizing its use (15).

In conclusion, we hope that our article, the above letters, and the additional information that has been provided here will serve to bring Cushing's contributions to the history of anesthesia to a new generation of anesthetists.

Nicholas P. Hirsch, MB, BS, FFARCS

Gary B. Smith, BM, FFARCS
28 St. George's Drive
London SW1V 4BN, England

References

1. Vesalius A. Some observations on the dissection of living animals. *De Corporis Humanis Fabrica* 1555;7:chapter 9.
2. Hooke R. An account of an experiment made by R. Hooke of preserving animals alive by blowing through their lungs with bellows. *Phil Trans Roy Soc* 1667;2:539.
3. Matas R. On the management of acute traumatic pneumothorax. *Ann Surg* 1899;29:409-34.
4. Cushing H, Branch JR. Experimental and clinical notes on chronic valvular lesions in the dog and their possible relation to a future surgery of the cardiac valves. *J Med Res* 1907;17:471-85.
5. Tuffier T, Hallion L. Intrathoracic operations with artificial respiration by insufflation. *C R Soc Biol* 1896;48:951.
6. Tuffier T, Hallion L. On the regulation of intrabronchial pressure and anesthesia in artificial respiration by insufflation. *C R Soc Biol* 1896;48:1086.
7. Ringer S. Concerning the influence exerted by each of the constituents of the blood on the contraction of the ventricle. *J Physiol (London)* 1880/82;3:389-93.
8. Cushing H. Concerning the poisonous effect of pure sodium chloride solutions upon the nerve-muscle preparation. *Am J Physiol* 1901;6:77-90.
9. Cushing correspondence. Yale Medical Library.
10. Fulton JF. Harvey Cushing—a biography. Springfield, IL: Charles C. Thomas, 1946:217.
11. Vandam LD, Walter M, Boothby, M.D.—The wellsprings of anesthesiology. *N Engl J Med* 1967;276:558-63.
12. Shephard DAE. Harvey Cushing and anaesthesia. *Can Anaesth Soc J* 1965;2:431-42.
13. Moore FD. Harvey Cushing: general surgeon, biologist, professor. *J Neurosurg* 1969;31:262-70.
14. Fulton JF. The vision and daring of youth: the story of the introduction of surgical anesthesia. *Yale J Biol Med* 1946;19:207-16.
15. Cushing H. Some principles of cerebral surgery. *JAMA* 1909;52:184-192.

Naloxone-Morphine Synergism

To the Editor:

Paradoxical synergism between morphine and naloxone reported by Dailey et al. during intrathecal use of morphine

during labor (1) was explained on the basis of dual system hypothesis of pain perception by Gillman and Lichtigfeld (2). It is important to note that naloxone "synergism" was observed only by the investigator (Fig. 3 in reference 1) and not by the subjects (Fig. 2 in reference 1). Although the methodology (1) mentions that the observer scored pain relief, Figure 3 indicates the percentage of patients with pain relief rather than the mean score of pain relief. Such a calculation of percentage can be directly biased by sample size. The histogram (Fig. 3 in reference 1) showed that initially, and for the next 3 hr, the number of patients undelivered is greater in the naloxone group; and from the fifth to seventh hr, the number of undelivered patients is greater in the saline group. Apparently the sample size from which the percentage has been calculated has dictated whether the control or test group has better analgesia. Therefore it is questionable whether the data from Figure 3 did indeed represent a synergism.

Naloxone synergism can also be explained on the basis of its agonistic effects (3-6). Agonistic effects of naloxone are not exclusively based on dose but rather on multiple factors that include route of administration, nature of pain, premedications, and supplemental medications that influence the manifestation of agonistic and/or antagonistic effects of naloxone (4). Furthermore, naloxone may also be converted to morphinomimetic metabolites (7,8). Therefore both the data and the experimental design for their derivation must be considered in interpreting the phenomenon of synergism of naloxone with morphine.

Krishnaswami Ramabadran, PhD

Department of Pharmacology
Faculty of Medicine, National University of Singapore
Lower Kent Ridge, Singapore 0511

Mylarrao Bansinath, PhD

Department of Anesthesiology
School of Medicine
NYU Medical Center
New York, NY 10016

References

1. Dailey PA, Brookshire GL, Shnider SM, et al. The effect of naloxone associated with the intrathecal use of morphine in labor. *Anesth Analg* 1985;56:246-9.
2. Gillman MA, Lichtigfeld FJ. Naloxone-morphine synergism: support for dual system hypothesis of pain perception. *Anesth Analg* 1986;65:313.
3. Jacob JJC, Ramabadran K. Enhancement of a nociceptive reaction by opioid antagonists in mice. *Br J Pharmacol* 1978;64:91-8.
4. Jacob JJC, Ramabadran K. Role of opiate receptors and endogenous ligands in nociception. *Pharmacol Ther* 1981;14:177-96.
5. Levine J, Gordon NC, Fields HL. Naloxone dose dependently produces analgesia and hyperalgesia in postoperative pain. *Nature* 1979;278:740-1.
6. Zilm DH. Naloxone response in non-dependent man: effect on six physiological variables. *Neuropharmacology* 1980;19:591-5.
7. Rios L, Jacob JJC. Inhibition of inflammatory pain by naloxone and its N-methyl quaternary analogue. *Life Sci* 1982;31:1209-12.
8. Rios L, Jacob JJC. Local inhibition of inflammatory pain by naloxone and its N-methyl quaternary analogue. *Eur J Pharmacol* 1983;96:277-83.

Book Reviews

The Pharmacological Basis of Therapeutics (seventh edition)

A. Goodman Gilman, L. S. Goodman, A. Gilman, eds.
New York: Macmillan Publishing Co., Inc., 1986, 1837 pp, \$65.00.

Owing to the complex nature of modern medical procedures, the increasing number of patients with major organ failure, the wide spectrum of drugs patients receive before surgery, and the potential for serious drug interactions, the anesthesiologist must have detailed knowledge of clinical pharmacology. For the informed clinician and scholar, anesthesiology journals, pharmacology journals, and assorted textbooks are the required reading; the consummate consultant's library includes standard pharmacology texts as well as the *Physician's Desk Reference*. Goodman and Gilman's *The Pharmacological Basis of Therapeutics* has traditionally deserved a place in our personal and departmental library. This text provides an overview of the fundamentals of pharmacology and therapeutics, including the concepts of pharmacokinetics and pharmacodynamics, drug mechanisms, and drug toxicity. It organizes detailed information to give an in-depth evaluation of prototypic drugs. This information is particularly useful for those involved in undergraduate medical education.

The new seventh edition of this classic textbook of pharmacology, toxicology, and therapeutics has reportedly undergone a thorough updating of every chapter, with respect to the mechanism of action and rational use of older drugs and the addition of important new therapeutic agents. Some chapters seemingly have had major revisions. Others have had only the lightest touch. For example, I could detect little or no new information in the several chapters concerning general anesthetics and adjuncts. They appear largely word-for-word as in the sixth edition. The chapter on neuromuscular blocking agents mentions atracurium and vecuronium, but modern concepts of the prejunctional effects of relaxants or their channel-blocking effects are found only in the fine print. Drug interactions between the relaxants and the potent inhalation anesthetics are largely missing. Likewise, little is new in the chapter on local anesthetics other than the suggestions that bupivacaine is more cardiotoxic than lidocaine and that chlorprocaine has been associated with neurotoxicity. The chapter on narcotics provides a superb, in-depth discussion of morphine, but fen-

tanyl merits only a paragraph. The fentanyl analogs are not discussed. No comment is made on high-dose narcotic anesthesia. The chapter on sedative hypnotics discusses diazepam but not midazolam. Of note, diazepam is mentioned in several chapters: as a general anesthetic in one, as a sedative hypnotic in another, and as an anticonvulsive medication in still a third. This presentation seems somewhat artificial.

My citation of these omissions and commissions may be somewhat faultfinding. The nonanesthetic chapters are, in general, excellent. For example, the discussion of antihypertensive drugs, antiarrhythmic drugs, histamine, and polypeptides is complete and detailed. The chapter on drug addiction is superb. Omissions in these chapters are, to me, less obvious, but certainly this reviewer knows less about these areas. In all candor, I only skimmed through the later chapters on laxatives, antibiotics, malaria, and antifungal medications. They seemed complete. In fact, they contained more information than I ever wanted to know about some of these topics.

In my view, Goodman and Gilman is still "the" standard pharmacology reference book. It provides detailed information about standard drugs. It is well-written and lucid. My criticism should not be construed as totally pejorative—clearly a general pharmacology text cannot provide a treatise on all subjects that will be judged by consultants in all specialties.

D. Ryan Cook, MD
Professor of Anesthesiology and Pharmacology
University of Pittsburgh and Children's Hospital
Pittsburgh, PA 15213

The Heart: Physiology, Metabolism, Pharmacology and Therapy

Lional H. Opie. Orlando, FL: Grune and Stratton, Inc., 1984, 392 pp, \$55.00.

Lional Opie is Director of the Ischemic Heart Disease Research Unit and Professor of Cardiac Medicine at the University of Cape Town, South Africa. He started his book in 1973 while on sabbatical leave in Italy with Professor Maseri. His goal was to explain cardiac function to medical students, interns, residents, fellows in cardiology and clinical cardiologists. Believing that physiology and biochem-

istry of the heart are best understood when integrated with pathophysiology and pharmacology, he has produced a unique text and appropriate companion for his monograph, *Drugs for the Heart*. Will anesthesiologists be interested in his book? Yes, both those in clinical practice and in academia who want to thoroughly understand the heart and avoid pharmacologic catastrophes will find it valuable.

The book is cleverly organized into four sections. The first reviews the cellular basis of cardiac physiology and includes a discussion of heart cells and intracellular organelles. Beautifully illustrated diagrams and metabolic schemes are interspersed with electron microscopic plates of cardiac muscle, ventricular myocytes, and mitochondria. Opie attempts to show how an understanding of cellular metabolism is fundamental to an understanding of myocardial contractility and of the mode of action of β -adrenergic blockers, calcium channel antagonists, and load reducing agents. Ionic homeostasis is described, along with the role of sodium-potassium and calcium pumps and the regulation of sodium, potassium, and calcium channels, again with artfully illustrated diagrams. A proposed channel for magnesium is discussed. Finally, the cardiac pacemaker, the conduction system, calcium fluxes, and the linkage of cardiac function to agonist-receptor (substrate-enzyme) reactions by intracellular messengers are discussed.

The second section, on energy metabolism and ventricular function, traces the metabolic pathways of carbohydrates and lipids to the production of adenosine triphosphate (ATP) and explains the use of the resultant energy for myocardial contraction and movement of ions. The coronary circulation is discussed as the link between oxygen supply and demand.

The third section includes a lucid review of the autonomic nervous systems, β - and α -adrenoreceptor antagonists, vasodilators, calcium antagonists, digitalis, and sympathomimetic stimulants. The fundamental physiologic principles of oxygen supply and demand are used to explain the mechanism of action of cardiac drugs. Much of the material in this section is a repeat of information in *Drugs for the Heart*, but it is presented in more detail and with more numerous schematic representations.

The final section covers the pharmacologic therapy of hypertension, valvular heart disease, congestive heart failure, ischemic heart disease, and arrhythmias.

References at the end of each chapter are current. In addition, a small section entitled "New References" includes articles published in 1985.

Throughout the book, there is a quality of thought that makes the reader feel he or she is confronting a scientist of substantial intellectual capacity. The sentences are bold and strong, and the author doesn't hide his message between them. He often asks a simple yet unanswerable question, then proceeds to give the latest investigational information, factual or speculative. Occasionally, he throws in a vignette about investigators, such as Ringer or Krebs.

My enthusiasm for this book should not be misinterpreted. Despite the fact that it is well-written and easy to

read, many parts are complex. Just as proteins, carbohydrates, and fats have to be digested, some sections deserve rereading. Nevertheless, it's the kind of book I wish I had read in medical school or during my residency. Those who want more than superficial knowledge of the heart will appreciate it the most.

Carolyn J. Wilkinson, MD
Associate Professor of Anesthesia
Northwestern University Medical School
Chicago, IL 60611

Primer of Water, Electrolyte and Acid-Base Syndromes

Emanuel Goldberger. Philadelphia: Lea & Febiger, 1986, 414 pp, \$19.50.

Dr. Goldberger has done a remarkable job of constructing a very readable text out of a (usually) bone-dry subject. In its seventh edition since 1959, *A Primer of Water, Electrolyte and Acid-Base Syndromes* has the depth and breadth of an authoritative textbook, yet because of its format it can function as a convenient and eminently useable handbook for the student, clinical clerk, or houseofficer, as well as a valuable reference for the practicing physician.

Complex concepts are explained in lucid, coherent prose; practical and clinically relevant scenarios with problem-solving examples are plentiful. Though mostly a medically oriented book, its utility cuts across medical and surgical specialty boundaries both in content and context. This is exemplified by the concise and excellent treatment of such topics as SIADH, regulation of hyperalimentation constituents, and fluid management in burn patients.

Though otherwise quite comprehensive, there is very little that is specifically directed toward the domain of anesthesiology. One exception is a short section on the interpretation of blood pH during hypothermic anesthesia and surgery. Circumstances that are pertinent to the anesthesiologist such as induced respiratory alkalosis for neurosurgery, the effects of hyper- or hypoventilation on anesthesia, and acute changes in water and electrolyte balance (e.g., transurethral resection of the prostate (TURP) operations, protracted intrabdominal operations) are not addressed. These subjects are, of course, covered in most standard anesthesia texts and would be of such limited interest to the general reader as to add unnecessary length. As such this work does not strive to be the panacea for every medical specialist on the subject of water, electrolyte, and acid-base, but certainly contains the essentials for all practitioners.

With few exceptions the text is typographically correct and accurate. It is extremely well-referenced and indexed. This book would be of considerable value to medical students and houseofficers alike. It would be an excellent resource for board preparation and review and it would be a

valuable reference for veritably all practicing clinicians but has special appeal for the anesthesiologist.

In a word, this book is practical. It facilitates, and even makes pleasurable, the traditionally difficult and often tedious voyage through an absolutely fundamental area of clinical medicine. In so doing, Dr. Goldberger makes more discernible the "forest for the trees." In this case the "forest" is the patient. Dr. Goldberger's prefacing comment that "at the end of a needle there is a patient" is actualized by this notable contribution.

Perry G. Fine, MD
*Assistant Professor of Anesthesiology
University of Utah School of Medicine
Salt Lake City, UT 84132*

Intensive Care Medicine

J. M. Rippe, R. S. Irwin, J. S. Alpert, and J. E. Dalen, eds. Boston: Little Brown & Co., 1985, 1203 pp, \$85.00.

This text is well-organized and set in an attractive double column format, with good headings, readable type, a good index, and an ambitious approach to the problems of care in the ICU. The approach begins with an Atlas of Procedures in the ICU, followed by a system-oriented discussion of the disease processes to be seen there.

The editors note in their introduction that intensive care medicine is, in essence, advanced medicine. Their selection of section editors and authors supports this position; most are drawn from the top ranks of internal medicine in their institution. As one would expect from this group of authors, mechanisms of disease are presented in a well-rounded and detailed fashion. However, when it comes to details of therapy, the same cannot be said. This is unfortunate since much of therapy and the procedures needed to deliver it require a great deal of attention to the details needed for the avoidance of complications and to ensure the patient's welfare. As an example, the section on intubation could have included discussion of some of the aids to difficult intubation and changing of tubes using such things as intubation guides, fiberoptic stylettes, and bronchoscopes; description of some of the newer tube fixation devices; and more detailed criteria for extubation, particularly for patients with significant intercurrent cardiac disease. The endotracheal tube cuff discussion could have included some detail of the factors contributing to tracheomalacia, such as the capillary perfusion pressure in the trachea and of the devices available to limit cuff pressures such as the Shiley or Lanz valves. A Shiley valve is shown attached to a tube, but no acknowledgement or explanation accompanies the illustration.

The section on CVP cannulation describes a catheter through needle technique that is now less common with the use of the small finder needles, cannulae, guide wires, and catheters that have been available in kit form for some time.

The suggestion that naloxone be used for the treatment of respiratory depression after narcotic administration in patients with myocardial infarction should not have been made without some amplification of the potential risks of autonomic activation and the dosages involved. Some amplification of other risks might also have been included, e.g., the use of verapamil with β -blockers without pacemaker capability or the infusion of potentially necrotizing substances through distal veins.

The section on dysrhythmias might have benefited by the inclusion of the information concerning potassium and magnesium referred to in later chapters. Similarly, the discussion of nasotracheal intubation would have been more complete with the inclusion of the later material describing the associated risks of sinusitis.

There are other problems. One is the failure to mention the risk in the use of dorsalis pedis arterial lines in patients with peripheral vascular disease. Another is the suggestion that pulmonary artery balloons be inflated slowly, implying that this would be safer, ignoring the fact that these balloons inflate almost instantaneously and exert extremely high lateral wall pressures.

The problems of multiple authorship, particularly when not all have been intimately involved in day-to-day of care in the ICU; the lack of detail for some of the specifics of intervention and therapy; and the exclusion of some of the more common postoperative surgical problems such as those seen after open heart surgery restrict the value of the text to its presentation of mechanisms and an overview of therapy for the disease processes seen in the ICU.

Donald C. Finlayson, MD, FRCP(C)
*Director, Division of Critical Care Medicine in the Department
of Anesthesiology
Emory University School of Medicine
Atlanta, GA 30322*

Anaesthetic Equipment: Physical Principles and Maintenance (second edition)

C. S. Ward. London: Ballière Tindall, 1985, 371 pp, \$45.95.

This book has been written for the anesthetist, operating room technician, anesthetic nurse, and intensive care unit staff. The text outlines the function of various items of anesthetic apparatus and how they should be maintained. The book is easy to read with many explicit diagrams and clear photographs.

The first two chapters describe the physical and mechanical properties upon which anesthetic apparatus is based. Ensuing chapters cover anesthetic gas supply, ventilators, vaporizers, and most of the equipment the anesthetist will encounter in his or her day-to-day working environment. Additional chapters in this new edition include the important areas of dental chair anesthesia and pollution control, which are welcomed.

Overall, this book provides the anesthetist in training with practical details of the equipment he or she uses. The

causes of life-threatening mechanical failures are described, but surprisingly, the chapter on the hazards and psychology of accidents is very short and deserves more detailed discussion. The book cannot be regarded as a substitute for the classic texts in areas such as physics and anesthetic principles or ventilation and circuits. However, it is an excellent introduction to equipment for the junior anesthetist and parts of the book will be of considerable benefit to technicians and nurses. The leaning towards practice in Great Britain may reduce its appeal to the North American practitioner.

Philip T. Conroi, MD
Visiting Assistant Professor of Anesthesiology
University of North Carolina at Chapel Hill
Chapel Hill, NC 27514

Books Received

Receipt of the following books from their publishers is acknowledged with thanks. Selected books from this list will be reviewed in the future.

Davis JE, ed. Major Ambulatory Surgery. Baltimore: Williams and Wilkins, 1986, 494 pp, \$69.50.

Smith NT, Corbascio AN, eds. Drug Interactions in Anesthesia, 2nd edition. Philadelphia: Lea & Febiger, 1986, 482 pp, \$47.50.

Gravenstein JS, Peter K, eds. Extracorporeal Shock-Wave Lithotripsy for Renal Stone Disease. Stoneham, MA: Butterworth Publishers, 1986, 158 pp, \$19.96.

Levitzky MG. Pulmonary Physiology, 2nd edition. New York: McGraw-Hill, 1986, 276 pp, \$17.96.

ERRATUM

Coburn CM, Eger EI II. The Partial Pressure of Isoflurane or Halothane Does Not Affect Their Solubility in Blood: Inhaled Anesthetics Obey Henry's Law. Volume 65, Number 6, June 1986.

Page 673, Table 1, bottom row of data

The partition coefficients listed for halothane are incorrect.

CHANGE	Saline		Blood	
Partition coefficient	0.54 ± 0.02	0.53 ± 0.03	0.51 ± 0.09	1.56 ± 0.08
TO READ				
Partition coefficient	0.77 ± 0.04	0.76 ± 0.03	2.62 ± 0.27	2.66 ± 0.18

***One agent
has inspired a new
way of looking at
surgical muscle
relaxation.***

TRACRIUM[®] INJECTION

(atracurium besylate)

Intrinsically predictable, uncommonly flexible

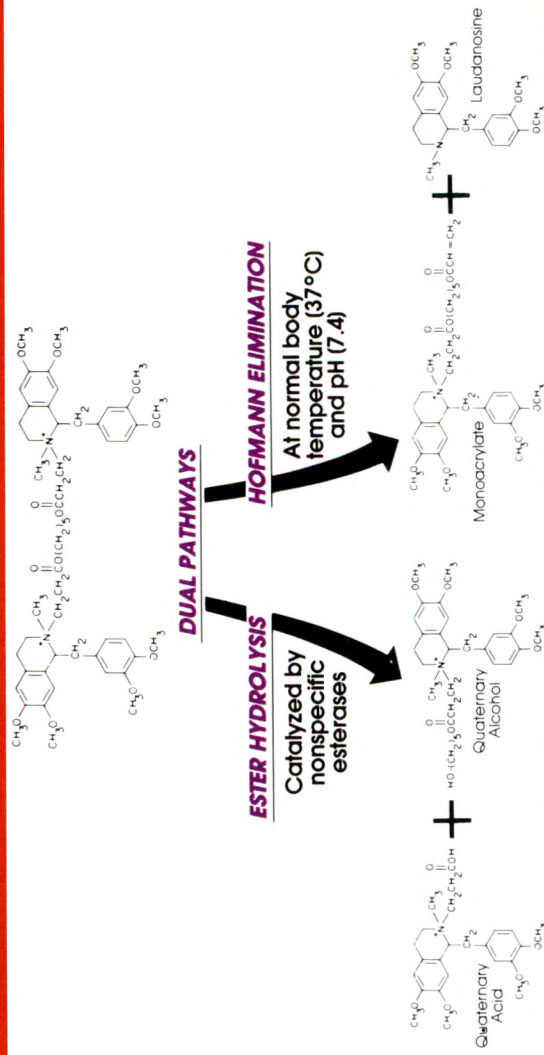
● **Predictable because it doesn't accumulate.**

Equal maintenance doses of Tracrium, repeated at equal time intervals during surgery, have no cumulative effect on recovery time.

Once recovery begins following the last administered dose, it is relatively rapid and independent of the total dose. Thus, you need not calculate progressively smaller doses of Tracrium for repeat administration. Recovery is more consistent and predictable.

● **Metabolized independent of liver or kidney function.**

Tracrium[®] Injection (atracurium besylate) is not dependent on kidney or liver function for elimination. It is inactivated by two nonoxidative pathways:



● **Few cardiovascular effects.**

At recommended doses, Tracrium produces virtually no clinically significant cardiovascular hemodynamic effects — an advantage over tubocurarine, metocurine, and pancuronium in patients with compromised cardiac ability or cardiac risk.

● **Minimal histamine release at recommended doses.**

Tracrium Injection is a less potent histamine releaser than d-tubocurarine or metocurine.

Clinically significant changes (about 200% of control) in arterial pressure and heart rate resulting from histamine release occur well within the clinical dosage range (at ED_{95}) for curare, at the upper limits of the clinical dosage range (at $2 \times ED_{95}$) for metocurine, and outside the clinical dosage range (at $3 \times ED_{95}$) for atracurium.¹

● **No mixing. Ready to use.**

Good stability.

Tracrium is easily administered, requiring no premixing or measuring. At room temperature ($25^{\circ}C$), potency loss is 5% per month.




Reference:
1. Basta SJ, Savarese JJ, Ali HH, et al: Histamine-releasing potencies of atracurium besylate (BW 33A), metocurine, and d-tubocurarine, abstracted. *Anesthesiology* 1982;57:A261.

Please see brief summary of prescribing information on following page.



**Gives you
superior control
and predictability**

TRACRIUM[®] INJECTION
(atracurium besylate)

 **Burroughs Wellcome Co.**
Research Triangle Park
North Carolina 27709

New Use: Infants from one month of age

TRACRIUM® INJECTION (atracurium besylate)

This drug should be used only by adequately trained individuals familiar with its actions, characteristics, and hazards.

DESCRIPTION: Tracrium (atracurium besylate) is an intermediate-duration, nondepolarizing, skeletal muscle relaxant for intravenous administration.

INDICATIONS AND USAGE: Tracrium is indicated, as an adjunct to general anesthesia, to facilitate endotracheal intubation and to provide skeletal muscle relaxation during surgery or mechanical ventilation.

CONTRAINDICATIONS: Tracrium is contraindicated in patients known to have a hypersensitivity to it.

WARNINGS: TRACRIUM SHOULD BE USED ONLY BY THOSE SKILLED IN AIRWAY MANAGEMENT AND RESPIRATORY SUPPORT.

DO NOT GIVE TRACRIUM BY INTRAMUSCULAR ADMINISTRATION.

Tracrium has no known effect on consciousness, pain threshold, or cerebration. It should be used only with adequate anesthesia.

Tracrium Injection should not be mixed with alkaline solutions (e.g., barbiturate solutions) in the same syringe or administered simultaneously during intravenous infusion through the same needle. Depending on the resultant pH of such mixtures, Tracrium may be inactivated and a free acid may be precipitated.

PRECAUTIONS:

General: Although Tracrium is a less potent histamine releaser than d-tubocurarine or metocurine, the possibility of substantial histamine release in sensitive individuals must be considered. Special caution should be exercised in administering Tracrium to patients in whom substantial histamine release would be especially hazardous (e.g., patients with clinically significant cardiovascular disease) and in patients with any history (e.g., severe anaphylactoid reactions or asthma) suggesting a greater risk of histamine release. In these patients, the recommended initial Tracrium dose is lower (0.3 to 0.4 mg/kg) than for other patients and should be administered slowly or in divided doses over one minute.

Since Tracrium has no clinically significant effects on heart rate in the recommended dosage range, it will not counteract the bradycardia produced by many anesthetic agents or vagal stimulation. As a result, bradycardia during anesthesia may be more common with Tracrium than with other muscle relaxants.

Tracrium may have profound effects in patients with myasthenia gravis, Eaton-Lambert syndrome or other neuromuscular diseases or in patients with severe electrolyte disorders or carcinomatosis.

The safety of Tracrium has not been established in patients with bronchial asthma.

Drug Interactions: The neuromuscular blocking action of Tracrium may be enhanced by enflurane, isoflurane, halothane, certain antibiotics, especially the aminoglycosides and polymyxins; lithium; magnesium salts; procainamide; or quindine.

If other muscle relaxants are used during the same procedure, the possibility of a synergistic or antagonist effect should be considered.

Prior administration of succinylcholine does not enhance the duration, but quickens the onset and may increase the depth of neuromuscular blockade induced by Tracrium. Tracrium should not be administered until a patient has recovered from succinylcholine-induced neuromuscular blockade.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Carcinogenesis and fertility studies have not been performed. Atracurium was evaluated in a battery of three short term mutagenicity tests. It was non-mutagenic in both the Ames Salmonella assay at concentrations up to 1000 µg/plate, and in a rat bone marrow cytogenetic assay at up to paralyzing doses. A positive response was observed in the mouse lymphoma assay under conditions (80 and 100 µg/ml, in the absence of metabolic activation) which killed over 80% of the treated cells; there was no mutagenicity at 60 µg/ml and lower concentrations which killed up to half of the treated cells. A far weaker response was observed in the presence of metabolic activation at concentrations (1200 µg/ml and higher) which also killed over 80% of the treated cells. Mutagenicity testing is intended to simulate chronic (years to lifetime) exposure in an effort to determine potential carcinogenicity. Thus, a single positive mutagenicity response for a drug used infrequently and/or briefly is of questionable clinical relevance.

Pregnancy: Teratogenic Effects: Pregnancy Category C. Tracrium has been shown to be potentially teratogenic in rabbits when given in doses up to approximately one-half the human dose. There are no adequate and well-controlled studies in pregnant women. Tracrium should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Labor and Delivery: It is not known whether muscle relaxants administered during vaginal delivery have immediate or delayed adverse effects on the fetus or increase the likelihood that resuscitation of the newborn will be necessary. The possibility that forceps delivery will be necessary may increase.

Tracrium (0.3 mg/kg) has been administered to 26 pregnant women during delivery by cesarean section. No harmful effects were attributable to Tracrium in any of the

newborn infants, although small amounts of Tracrium were shown to cross the placental barrier. The possibility of respiratory depression in the newborn infant should always be considered following cesarean section during which a neuromuscular blocking agent has been administered. In patients receiving magnesium sulfate, the reversal of neuromuscular blockade may be unsatisfactory and Tracrium dose should be lowered as indicated.

Nursing Mothers: It is not known whether this drug is excreted in human milk. Caution should be exercised when Tracrium is administered to a nursing woman.

Pediatric Use: Safety and effectiveness in children below the age of 1 month have not been established.

ADVERSE REACTIONS: Tracrium produced few adverse reactions during extensive clinical trials, most of which were suggestive of histamine release (see PRECAUTIONS section). The overall incidence of clinically important adverse reactions was 7/875 or 0.8%.

Approximately one million patients received Tracrium during the first year following introduction to the U.S. market in December, 1983. Spontaneously reported adverse reactions were uncommon (approximately 0.02%). The following adverse reactions are among those most frequently reported, but there are insufficient data to support an estimate of their incidence:

Musculoskeletal: Inadequate block, prolonged block

Cardiovascular: Hypotension, vasodilatation (flushing), tachycardia, bradycardia

Respiratory: Dyspnea, bronchospasm, laryngospasm

Integumentary: Rash, urticaria, reaction at injection site

DOSAGE AND ADMINISTRATION: Tracrium should be administered intravenously. DO NOT GIVE TRACRIUM BY INTRAMUSCULAR ADMINISTRATION.

Adults: A Tracrium dose of 0.4 to 0.5 mg/kg (1.7-2.2 times the ED₅₀), given as an intravenous bolus injection, is the recommended initial dose for most patients. With this dose, good or excellent conditions for nonemergency intubation can be expected in 2 to 2.5 minutes in most patients, with maximum neuromuscular blockade achieved approximately 3 to 5 minutes after injection. Clinically acceptable neuromuscular blockade under balanced anesthesia generally lasts 20 to 35 minutes; recovery to 25% of control is achieved approximately 35 to 45 minutes after injection, and recovery is usually 95% complete approximately 60 minutes after injection.

Tracrium is potentiated by isoflurane or enflurane anesthesia. The same initial Tracrium dose of 0.4 to 0.5 mg/kg may be used for intubation prior to administration of these inhalation agents; however, if Tracrium is first administered under steady state of isoflurane or enflurane, the initial Tracrium dose should be reduced by approximately one-third, i.e., to 0.25 to 0.35 mg/kg, with halothane, which has only a marginal (approximately 20%) potentiating effect on Tracrium, smaller dosage reductions may be considered.

Tracrium doses of 0.08 to 0.10 mg/kg are recommended for maintenance of neuromuscular blockade during prolonged surgical procedures. The first maintenance dose will generally be required 20 to 45 minutes after the initial Tracrium injection, but the need for maintenance doses should be determined by clinical criteria. Maintenance doses may be administered at relatively regular intervals for each patient, ranging approximately from 15 to 25 minutes under balanced anesthesia, slightly longer under isoflurane or enflurane.

Children and Infants: No Tracrium dosage adjustments are required for pediatric patients two years of age or older.

A Tracrium dose of 0.3 to 0.4 mg/kg is recommended as the

initial dose for infants (1 month to 2 years of age) under halothane anesthesia. Maintenance doses may be required with slightly greater frequency in infants and children than in adults.

Special Considerations: An initial Tracrium dose of 0.3 to 0.4 mg/kg, given slowly or in divided doses over one minute, is recommended for adults, children, or infants with significant cardiovascular disease and for adults, children, or infants with any history (e.g., severe anaphylactoid reactions or asthma) suggesting a greater risk of histamine release.

Dosage reductions must be considered also in patients with neuromuscular disease, severe electrolyte disorders, or carcinomatosis in which potentiation of neuromuscular blockade or difficulties with reversal have been demonstrated. No Tracrium dosage adjustments are required for patients with renal disease.

An initial Tracrium dose of 0.3 to 0.4 mg/kg is recommended for adults following the use of succinylcholine for intubation under balanced anesthesia. Further reductions may be desirable with the use of potent inhalation anesthetics. The patient should be permitted to recover from the effects of succinylcholine prior to Tracrium administration. Insufficient data are available for recommendation of a specific initial Tracrium dose for administration following the use of succinylcholine in children and infants.

U.S. Patent No. 4179507

Printed in U.S.A.

For the latest facts about
TRACRIUM® INJECTION
(atracurium besylate)

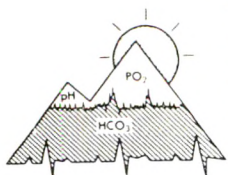
Join us at
The New York State
Society for Anesthesiologists PGA
New York, NY
December 13-17, 1986



Burroughs Wellcome Co.
Research Triangle Park
North Carolina 27709

TRACRIUM INJECTION

(atracurium besylate)



**SIXTH ANNUAL
CANADIAN WINTER
ANAESTHESIA
MEETING**
Quebec City, Que
February 22-27, 1987

The Scientific Program includes a wide range of subjects: O.B. Anesthesia, I.C.U., Pediatric Anesthesia, Intraoperative Problems, and Trauma from the E.R. to the O.R.

This Program is approved for A.M.A. Category 1 C.M.E. Credits.

The Scientific Program has been arranged to provide ample time to explore this charming winter setting.

For further information, please write to:

Programme Chairman
Canadian Winter Anaesthesia Meeting
Department of Anaesthesia, Room 2303
The Hospital for Sick Children,
555 University Avenue,
Toronto, Ont. Canada M5G 1X8
or call: (416) 598-7445

OPPORTUNITIES IN DALLAS

ANESTHESIOLOGY

CIGNA Healthplan, one of the nation's largest investor-owned health maintenance organizations, is selecting qualified physicians to join our growing Dallas Healthplan. As one of the highly respected physicians with CIGNA Healthplan, you can have the kind of practice and Sunbelt lifestyle you want without the distracting administrative details you don't want. In addition to the competitive salary structure and exceptional benefits program we offer, you will enjoy **paid malpractice insurance coverage**, scheduled working hours, pension and retirement benefits, professional development time and funding, and paid vacations.

For confidential consideration, send your c.v. to the Director of Physician Recruitment, CIGNA Healthplan of Texas, Inc., Dept. 12AA, P.O. Box 202575, Dallas, TX 75220, (214) 964-4422.

Equal Opportunity
Employer M/F/V/H

CIGNA

Imagine

An O.R. Monitor That

- **Monitors two ECG's, three invasive pressures, two temps and pulse.**
- **Displays waveforms, trends and text on a high resolution color display.**
- **Integrates data from existing equipment such as CO₂, SaO₂, NIBP, etc.**
- **Records waveforms and trends on a built-in, state-of-the-art, multi-function recorder.**
- **Simple to use.**

**And All For A Price
Less Than \$10,000!**

Introducing the PB240

Evolving standards of care demand that an increasing number of patient parameters be monitored. The result is a growing network of instrumentation surrounding the anesthesiologist creating clutter and confusion in the operating room. "Monitoring the monitors" takes time that could be better used to monitor the patient.

To reverse this trend, the PB240 monitors basic physiological parameters and combines data from external devices into a single central display and integrated monitoring system. All data is trended for four hours - external data, as well as monitored data - and can be displayed and recorded as required. Its powerful software-based design allows the PB240 to be upgraded and grow with your needs.

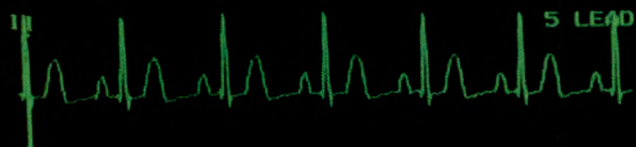
Best of all, the PB240 is easy to use and easy on your budget too!

For further information or to arrange a demonstration, contact your nearest sales representative or call 1-800-255-6773.

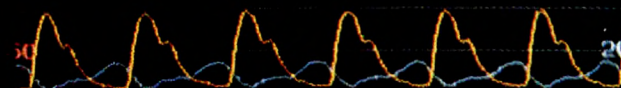
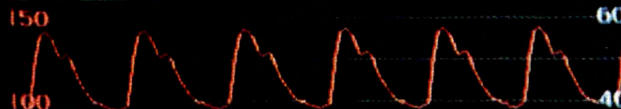


PURITAN-BENNETT CORPORATION

PB 240



CO2



P1 142/95 (114) HR 80

P2 17/11 (14)

P3 28/11 (17)

CO2 5.0 O2 21 N2O 1

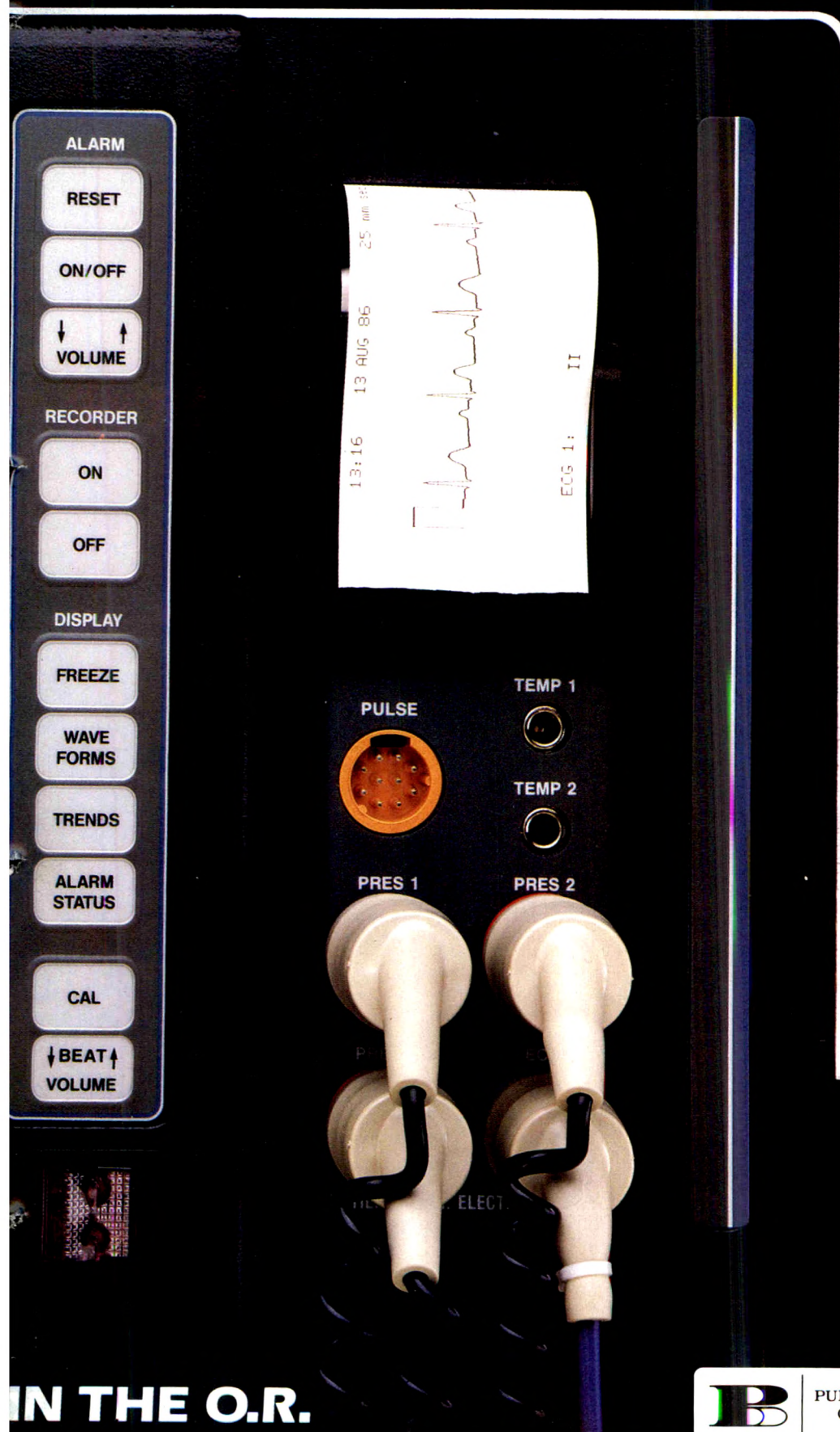
14:45

ECG ADJUST MVFM2 NEXT PRES. ZERO PRES. ADJUST TREND MARK



HELPING YOU MANAGE RISK

Operating Room Monitor



ADVANCED MONITORING CAPABILITY

Two ECG leads
Three Direct Pressures
Two Temperatures
Pulse
Extended Input Output

LARGE COLOR MONITOR

Five Waveforms
High Resolution
Color Coded
Bright
Easy to Read

EXTENDED DISPLAYS

Trends of all Parameters
Graphic Alarm and
Patient Status

IN THE O.R.



PURITAN-BENNETT
CORPORATION

Boston Division
265 Ballardvale Street
Wilmington, MA 01887
(617) 657-8650

Classified Advertising

PERMANENT POSITION WANTED

CRNA—experienced, wishes busy situation, solo or group, best of remuneration. 1-800-521-6750.

MDAS OR CRNAS: TRANS-AMERICAN ANESTHETISTS, WEST

Temporary or Permanent MDAs, CRNAs, ready to serve you, up-to-date skills, co-operative, licensed, insured professionals caring about you. Call 1-800-762-1258, Box 24432, Colorado Springs, CO 80918, or 303-598-2788 (CO).

ANESTHESIOLOGISTS

Excellent, prequalified individuals available to join your group on a career or temporary basis. For more information please contact: Southwest Anesthesia Services, PO Box 5719, Santa Fe, New Mexico 87502, (505) 983-7371.

ROCKY MTS./SOUTHWEST

We have career and temporary positions available from solo to large group practice in the Rocky Mts. and Southwest. Expenses paid; partnerships usually available. Please contact Southwest Anesthesia Services, PO Box 5719, Santa Fe, NM 87501. (505) 983-7371.

800-FAST GAS: WORLDWIDE ANESTHESIA

Have you got knock and pings in your Anesthesia Department? Whether it's a short or long-term staff shortage . . . we've got quality MDs and CRNAs to get your program running smoothly! 1-800-327-8427 Worldwide Anesthesia, John Paju, President.

TUTORING FOR WRITTEN AND ORAL BOARD EXAMS:

Individual or small group sessions given in New York City, San Francisco, and Palm Springs. Unique approach to development of test-taking skills, including mock orals. Basic science emphasis. Call 415-321-1117 or reply to Box K23, % *Anesthesia and Analgesia*, Desk Editorial, 52 Vanderbilt Avenue, New York, NY 10017. Include phone number in response.

PRIVATE TUTORING AVAILABLE FOR WRITTEN AND ORAL BOARD EXAMS

Send name, address, and phone to Box ANA 5-84-E, % *Anesthesia and Analgesia*, Desk Editorial, Elsevier Science Publishing Co., Inc., 52 Vanderbilt Avenue, New York, NY 10017.

TEXAS

Pediatric Anesthesiologist. Excellent opportunity available for BC/BE pediatric anesthesiologist with minimum 1 yr pediatric fellowship. Be second person in exciting practice serving two children's hospitals. Experience in pediatric cardiology, PICU, NICU, or pulmonary helpful. Hospitals offer all subspecialties. Must be eligible for Texas license (FLEX required). Benefits include competitive salary, malpractice, profit sharing leading to partnership. If living in a city filled with cultural, recreational, and academic facilities while practicing in two of the SW's finest hospitals appeals to you, submit a CV with three references to: Search Director, PO Box 2138, Fort Worth, TX 76113.

ALABAMA

Several immediate openings. We are consultants for anesthesiologists and charge no placement fees. Send reply in confidence to Medical Management, Inc., PO Drawer 7308, Montgomery, AL 36107.

ANESTHESIOLOGIST SEEKING CHAIRMAN

for established anesthesia department in 400-bed suburban Chicago, Illinois hospital. All surgical specialties represented, including open heart. Must be board certified with 7 yr minimum in academic environment. Excellent financial arrangements. Send CV to CSS Associates, 6819 Winston Drive, Tinley Park, Illinois 60477.

COOK COUNTY HOSPITAL DEPARTMENT OF ANESTHESIOLOGY

An opening for a Division Chairman of Pediatric Anesthesiology. Must be board certified in anesthesiology and have at least two yr experience in pediatric anesthesiology. Excellent administrative and teaching abilities. Competitive salary and excellent fringe benefits. Send CV to or call Dr. Radha Kartha, Acting Chairperson, Department of Anesthesiology, Cook County Hospital, 1925 West Harrison Street, Chicago, IL 60612. (312) 633-6176.

ANESTHESIOLOGIST

35 yr old. Board eligible. Available immediately. Proficient in all types of anesthesia. 3 yr experience after 4 yr of residency training. Respond to Box Y1, % *Anesthesia and Analgesia*, Desk Editorial, Elsevier Science Publishing Company, 52 Vanderbilt Avenue, New York, NY 10017.

UPPER MIDWEST

Board Certified/Board Eligible Anesthesiologist to direct anesthesia services for a modern and fully equipped 129-bed hospital. Minimum cash-collections of \$175,000 will be provided with other incentives. No open hearts or neuro. Response confidential. Reply to Box Z4, % *Anesthesia and Analgesia*, Elsevier Science Publishing Company, Inc., 52 Vanderbilt Avenue, New York, NY 10017.

LOUISIANA

Excellent opportunity for a board certified Anesthesiologist in a full time position, in South Louisiana. 55 miles from New Orleans, closely associated with the Ochsner Medical Foundation located in New Orleans. Salary very competitive, with superb fringe benefits. Contact Harry J. McGaw, MD, Medical Director, South Louisiana Medical Center, 1978 Industrial Blvd, Houma, LA 70363. Or phone (504) 873-1285.

STAFF ANESTHESIOLOGIST

750-bed medical school affiliated with Veterans Administration Medical Center. All types of major surgery except open heart. Board certification and full licensure required. Staff consists of 4 Anesthesiologist and 10 CRNAs. Federal benefits package. Send CV to Donald J. Mahler, MD, Chief Anesthesiology (112), VA Medical Center, 150 South Huntington Avenue, Boston, MA 02130. An equal opportunity employer.

CLASSIFIED ADS

Anesthesia and Analgesia makes available classified advertising space for those interested in obtaining positions, or wishing to announce meetings, postgraduate courses, or other events. Display space (minimum 1/4 page) is also available through Pharmaceutical Media, Inc. Rates for classified advertising: **\$1.00 per word, minimum twenty words. Additional fee of \$12.00 for box number ads.** Copy deadline 7 weeks prior to publication, e.g., for the March issue, copy should be received by the 1st of January. Full payment or institutional purchase order must accompany the copy for each ad. Ads received without a check or purchase order will be returned. Ad copy, subject to acceptance by publisher, should be typed double-spaced and mailed in duplicate to:
Anesthesia and Analgesia
Desk Editorial
Classified Ads
Elsevier Science Publishing Co., Inc.
52 Vanderbilt Avenue, New York, NY 10017.
Make checks payable to Elsevier Science Publishing Co., Inc.

GEORGIA

The Department of Anesthesiology at the Medical College of Georgia in Augusta, Georgia, has been granted two additional openings for PGY2 and PGY4 positions to begin in January 1987. The program is approved by the Council on Medical Education of the American Medical Association. Residents are required to participate in the annual ABA/ASA In-Training Examination. EEO Employer/Affirmative Action. Call (404) 828-3871 or write for application packet: Dan C. Martin, MD, Program Director, Department of Anesthesiology, Medical College of Georgia, Augusta, Georgia 30912.

NORTH CAROLINA

Temporary and permanent BE/BC anesthesiologists needed to join fee-for-service group in small community in heart of Blue Ridge Mtns. Salary first year. Send inquiries and CV to Watauga Anesthesia Associates, PA, 301 Birch St, Boone, NC 28607.

SOUTHWESTERN PA ANESTHESIOLOGIST

BE/BC to join group. All except open heart. Opening immediately. Excellent compensation and future for right person. Response confidential. Pittsburgh area. Submit CV to Box L26, % *Anesthesia and Analgesia*, Desk Editorial, Elsevier Science Publishing Company, 52 Vanderbilt Avenue, New York, NY 10017.

IOWA

University of Iowa, Department of Anesthesia. Faculty positions, all ranks. Excellent research facilities. Senior advice/consultation readily available. Must be eligible for Iowa medical licensure. Submit curriculum vitae to John H. Tinker, MD, Professor and Head, Department of Anesthesia, University of Iowa, Iowa City, IA 52242. The University of Iowa is an Equal Opportunity/Affirmative Action Employer.

NEW YORK: PEDIATRIC ANESTHESIOLOGIST

Expanding division of pediatric anesthesia, Department of Anesthesiology, Columbia University College of Physicians and Surgeons, is seeking individuals at the Assistant Professor/Associate Professor level with training in anesthesia and pediatrics. Division responsibilities are in the operating room and intensive care unit. Applicants should possess board certification or eligibility, excellent clinical and teaching skills as well as research interests. Interested individuals should reply to: Peter Rothstein, MD, Director, Division of Pediatric Anesthesia, Box 62, Babies Hospital, 622 West 168th Street, New York, NY 10032. Columbia University takes affirmative action to ensure equal opportunity.

INDIANA

A position is available for a pediatric anesthesiologist at the assistant or associate professor level in the Department of Anesthesia, Indiana University School of Medicine. Candidates must have completed a specialized year in pediatric anesthesia and be in the examination system or board certified. Please send a curriculum vitae to Robert K. Stoelting, MD, Professor and Chairman, Department of Anesthesia, Fesler Hall Room 204, Indiana University School of Medicine, 1120 South Drive, Indianapolis, IN 46223. Indiana University is an Equal Opportunity Employer

INDIANA

Faculty positions are available at the Assistant and Associate Professor levels. All candidates for these positions must be in the examination system or board certified. Please send a curriculum vitae to Robert K. Stoelting, MD, Professor and Chairman, Department of Anesthesia, Fesler Hall, Room 204, Indiana University School of Medicine, 1120 South Drive, Indianapolis IN 46223. Indiana University is an Equal Opportunity Employer

CHIEF OF ANESTHESIA

to head department serving 280-bed community hospital in Baltimore. Board certification required with administrative experience preferred. Position includes active practice of anesthesiology and responsibility for quality assurance standards and smooth operation of anesthesia services in a busy OR. Reply to Box X59, % *Anesthesia and Analgesia*, Desk Editorial, Elsevier Science Publishing Company, 52 Vanderbilt Avenue, New York, NY 10017.

ANESTHESIOLOGIST WANTED

for East Central WI city on Lake Mich. Attractive Educational, Cultural and Recreational opportunities. Convenient to Metro Area and Med. School. Chas. Cave Assoc. PO Box 564, Waukesha, WI 53187. (414) 547-7069.

MAINE

BE/BC anesthesiologist to join group doing 13,000 cases/year, all specialties including open heart. Unique opportunity for excellent lifestyle in heart of Maine's year around vacationland, near University of Maine, competitive benefits, liberal vacation and progressive anesthesia practice. Preference to those with demonstrated skills or fellowship in pain management. Kindly forward resume to Box Z5, % *Anesthesia and Analgesia*, Desk Editorial, Elsevier Science Publishing Company, 52 Vanderbilt Avenue, New York, NY 10017.

CALIFORNIA: ANESTHESIOLOGIST

Full-time faculty position at the Associate/Full Professor level in expanding, young department with emphasis on teaching and research. Complete clinical services in one hospital. Prerequisites include board certified; meet California license requirements; clinical expertise in neuro, pain and/or pediatrics; demonstrated ability as a research scientist and ability to write scholarly articles. Send curriculum vitae, bibliography and names of five references to John H. Eisele, JR, MD, Anesthesiology Department, University of California, Davis, Medical Center, 2315 Stockton Blvd., Sacramento, CA 95817. Position open until filled but not later than January 31, 1987. We are an Equal Opportunity/Affirmative Action Employer.

MICHIGAN

BCBE recent AMG to join group of 4 anesthesiologists supervising CRNAs. Facility with peripheral nerve blocks and invasive monitoring very desirable. Generous salary and benefits first year with possibility of full partnership thereafter. One hour from Detroit on the shores of Lake Huron. Send resumes to Eric J. Robb, MD, Anesthesia Associates of Port Huron, PC, 929 Division Street, PO Box 1219, Port Huron, MI, 48060.

ARIZONA

University of Arizona is expanding the Department of Anesthesiology. Academic career potential great. Fellowship or research experience required. Job entails clinical teaching, investigative opportunities. Equal Employment Opportunity/Affirmative Action Employer. Contact Burnell R. Brown, Jr., MD, Anesthesiology Dept., Arizona Health Sciences Center, Tucson, AZ 85724. The closing date for applications is Nov. 30, 1986.

CERTIFIED OR BOARD ELIGIBLE ANESTHESIOLOGIST

to join large group at New York metropolitan area hospital. Salary first year. Full partnership by fifth year. Include CV with first response. Reply to Box R38, % *Anesthesia and Analgesia*, Desk Editorial, Elsevier Science Publishing Company, 52 Vanderbilt Ave, New York, NY 10017.

NORTH CAROLINA

Anesthesiologist (BE/BC) wanted for thriving anesthesia practice in eastern North Carolina coastal plains city of 25,000 to join group of one MDA and three CRNAs in 200-bed hospital. All surgical subspecialties except Neuro and OH. Send CV to Box X60, % *Anesthesia and Analgesia*, Elsevier Science Publishing Company, Desk Editorial, 52 Vanderbilt Avenue, New York, NY 10017.

MASSACHUSETTS

Continued expansion of the Anesthesiology Department at the University of Massachusetts Medical Center has created a need for additional staff in the department. Designated as a regional trauma center, the University Medical Center also performs over 500 open heart procedures a year. Additional departmental responsibilities include an important role in critical care and pain control. Please respond to: Gary W. Welch, MD, PhD, Chairman of Anesthesiology, University of Massachusetts Medical Center, 55 Lake Avenue North, Worcester, MA 01605. An affirmative action/equal opportunity employer.

CALIFORNIA

Anesthesiologist: Two full-time faculty positions at the Assistant/Associate Professor level in expanding, young department with emphasis on teaching and research. Complete clinical services in one hospital. Prerequisites: fellowship year or equivalent training in subspecialty area; board eligibility; meet California license requirements; ability to write scholarly articles and have a genuine commitment to inquiry. Women and minorities are encouraged to apply. Send curriculum vitae, bibliography, and *names of three references* to John H. Eisele Jr., MD, Anesthesiology Department, University of California, Davis, Medical Center, 2315

Stockton Blvd, Sacramento, CA 95817. Position open until filled but not later than December 31, 1986. We are an Equal Opportunity/Affirmative Action Employer.

ARIZONA

University of Arizona seeking academically oriented obstetric anesthesiologist to lead new program. Opportunities for research, clinical teaching, and career expansion. Equal Employment Opportunity/Affirmative Action Employer. Contact Burnell R. Brown Jr, MD, Anesthesiology Dept., Arizona Health Sciences Center, Tucson, AZ 85724. The closing date for applications is Nov. 30, 1986.

INDEX TO ADVERTISERS

American Critical Care	
Hespan	A22-A24
Anaquest	
Forane	A17-A20
Astra Pharmaceuticals	
Sterile-Pak	Cover 4
Burroughs Wellcome Co.	
Tracrium	A37-A40
Cigna Healthplan of Dallas, Inc.	
Employment Opportunities	A41
Classified Advertising	A44-A45
Cormed	
Cormed II	A21
The Hospital for Sick Children	
Continuing Education	A41
Janssen Pharmaceutica	
Sufenta	A6-A7
Kettering Software Systems, Inc.	
Anesthesia Software Package	A13
Nicolet Biomedical Instruments	
Neurotrac	A2
North American Drager	
Narkomed 3	A14-A15
Ohmeda	
Biox 3700	A36
Organon Pharmaceuticals	
Norcuron	A9-A12
Pavulon	Cover 2, Cover 3
Puritan-Bennett Corporation	
PB240 O.R. Monitor	A41-A43
Hoffman La Roche, Inc.	
Versed	A26-A35

Advertising Office: Pharmaceutical Media, Inc., 130 Madison Avenue, 6th Floor, New York 10016; Telephone: (212) 685-5010

Organon presents.

The new, distinctive Pavulon[®] vial for positive identification and handling ease.

- New functionally contoured vial speeds selection and helps assure positive identification.
- Easy-grip, no-slip design for better handling.



- Now there is one more reason to choose PAVULON[®], with over 14 years of successful clinical experience.



Pavulon[®]
(pancuronium bromide
injection)

Now...tangibly different.



The Procedure:

Administration of Parenteral
Solutions in a Sterile
Environment

The Problem:

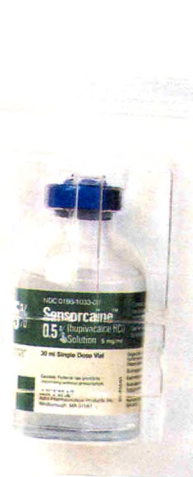
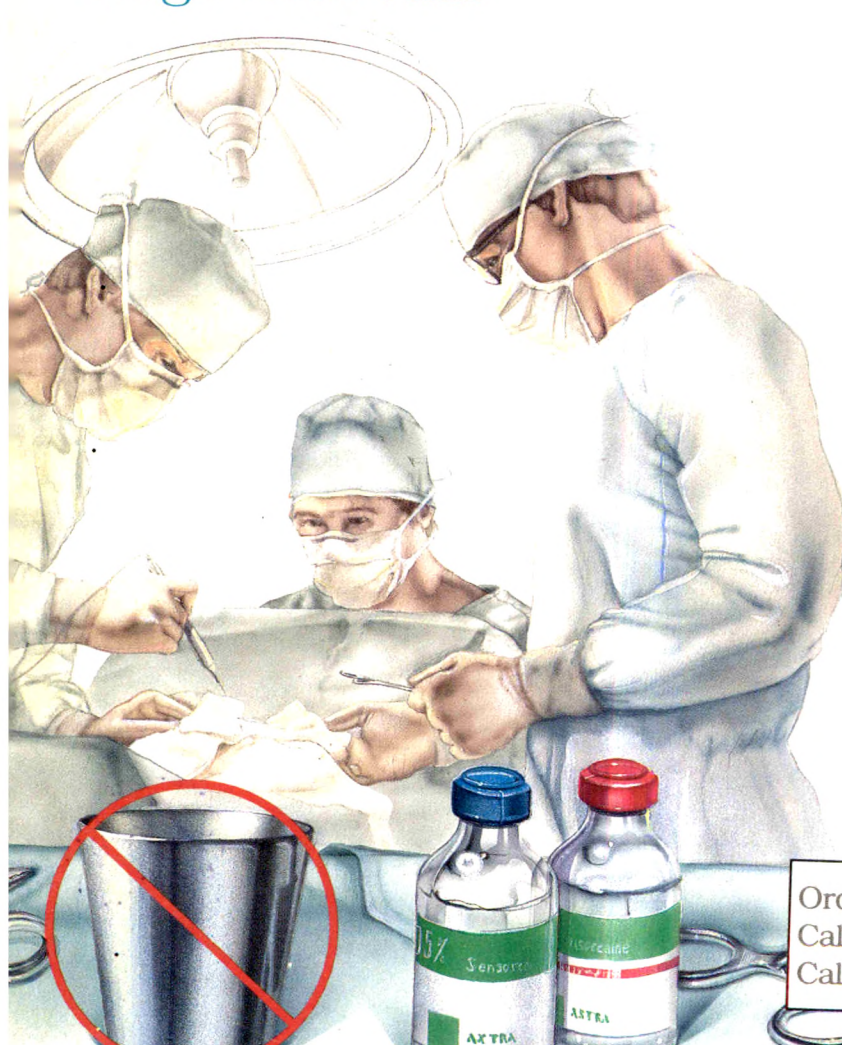
Potential Compromise of Sterile
Field and Confusion Caused by
Unlabeled Medicine Cups

The Product:

Sterile-Pak[®] Solutions in
Single-Dose Vials

The Profile:

- Pre-sterilized container exterior eliminate the time and expense of autoclaving
- Pre-labeled packaging for at-a-glance product identification
- Easy to open and ready to use in the sterile field
- Tamper-evident closures reveal previous entry
- Methylparaben-free solutions
- Available in both ampules and vials
- Available in several solutions and concentrations
- Proven Astra quality and reliability in product and service



Products that assist procedures
and solve problems.

Ordering Information:

Call 1-800-225-6333 for Professional Information
Call 1-800-225-4803 for Ordering Information

ISSN 0003-2999
Volume 65, Number 12, December 1986

Anesthesia and Analgesia

Acc.
16.12.87

Journal of the International Anesthesia Research Society
Oldest Publication in the Specialty—Established 1922



Organon presents:

The new, distinctive Pavulon® vial for positive identification and handling ease.

- New functionally contoured vial speeds selection and helps assure positive identification.
- Easy-grip, no-slip design for better handling.



- Now there is one more reason to choose PAVULON®, with over 14 years of successful clinical experience.



Pavulon®
(pancuronium bromide
injection)

Now...tangibly different.



Anesthesia and Analgesia

Journal of the International Anesthesia Research Society

3645 Warrensville Center Road, Cleveland, Ohio 44122 Telephones: (216) 295-1124 or 295-1130

Editorial Board

Editor in Chief

Nicholas M. Greene, MD, New Haven, Connecticut

Editors

David R. Bevan, MA, MB, BChir,
Montreal, Quebec, Canada

D. Ryan Cook, MD, Pittsburgh, Pennsylvania

Benjamin G. Covino, PhD, MD, Boston, Massachusetts

Norig Ellison, MD, Philadelphia, Pennsylvania

Mieczyslaw Finster, MD, New York, New York

Alison B. Froese, MD, Kingston, Ontario, Canada

Edward D. Miller Jr, MD, New York, NY

Walter S. Nimmo, MD, BSc, FRCP, FFARCS,
Sheffield, United Kingdom

Daniel M. Philbin, MD, Boston, Massachusetts

J. Gerald Reves, MD, Durham, North Carolina

Petter A. Steen, MD, Oslo, Norway

John H. Tinker, MD, Iowa City, Iowa

K.C. Wong, MD, PhD, Salt Lake City, Utah

Book Review Editor

Norig Ellison, MD, Philadelphia, Pennsylvania

Editorial correspondence and manuscripts should be addressed to: NICHOLAS M. GREENE, MD, Editor in Chief, *Anesthesia and Analgesia*, Yale University School of Medicine, 333 Cedar Street, New Haven, Connecticut 06510 (Telephone: 203-785-4703). For information concerning preparation of manuscripts see "A Guide for Authors" published quarterly in the Journal. All articles published in this Journal become the property of the International Anesthesia Research Society. Reproduction in whole or part is not permitted except by written consent of the publisher and the author.

Books for review should be sent directly to the Book Review Editor, NORIG ELLISON, MD, Department of Anesthesia, University of Pennsylvania, Philadelphia, Pennsylvania 19104.

Reprints: For single copies, write directly to the senior author at the address listed on the title page. Quantity orders (minimum 100) processed through ELSEVIER SCIENCE PUBLISHING CO, INC, 52 Vanderbilt Avenue, New York, NY 10017, prices on request.

The International Anesthesia Research Society is a nonprofit, scientific, and educational corporation in the state of Ohio. Members of the Board of Trustees of the Society are: Douglas B. Craig, MD, Bruce F. Cullen, MD, E. Paul Didier, MD, Judith H. Donegan, MD, PhD, Noel W. Lawson, MD, John T. Martin, MD, Emerson A. Moffitt, MD, Dean H. Morrow, MD, Robert K. Stoeltig, MD, and John L. Waller, MD. Emeritus Trustees are: Paul R. Dumke, MD, Morris T. Nicholson, MD, B. B. Sankey, MD, and T. H. Seldon, MD.

Anesthesia and Analgesia (ISSN 0003-2999) is issued monthly for the IARS in one indexed volume per year by Elsevier Science Publishing Co, Inc, 52 Vanderbilt Avenue, New York, NY 10017. Printed in USA. © 1985 International Anesthesia Research Society. Second class postage paid at New York, NY and at additional offices.

Subscription information for 1986 applying to IARS members: USA and possessions, \$50.00 per year, in all other countries \$61.00. Membership is available to individuals with doctorate degrees in medicine, osteopathy, dentistry, veterinary medicine, or other disciplines who are engaged in active clinical practice of or research in anesthesiology. ASSOCIATE MEMBERSHIP is available to individuals certified, licensed, or accredited in anesthesia-related professions (CRNA, CRIT, RRT, Physician Assistant). EDUCATIONAL MEMBERSHIP (half the full member price) is available to interns, residents, students in nurse anesthesia and related training programs, for a 2- or 3-year period only upon completion of application including certification by applicant's program director.

All membership payments and correspondence regarding IARS member subscriptions should be sent to: Emerson A. Moffitt, MD, Executive Secretary, International Anesthesia Research Society, 3645 Warrensville Center Road, Cleveland, Ohio 44122.

Subscription information for 1986 applying to non-IARS members: Institutions, \$95.00; nonmember individuals, \$50.00. Outside of the USA and possessions, please add \$11.00 for surface postage and handling. For airmail, add \$40.00 in USA, Canada, and Mexico, \$23.00 for surface airlift to Europe, \$36.00 for surface airlift to Japan, and \$93.00 for airmail to the rest of the world. Postmaster: Send address changes to: *Anesthesia and Analgesia*, Elsevier Science Publishing Co, Inc, 52 Vanderbilt Avenue, New York, NY 10017.

Orders and inquiries regarding institutional and nonmember individual subscriptions should be directed to: Journals Fulfillment, Elsevier Science Publishing Co, Inc, 52 Vanderbilt Avenue, New York, NY 10017. Subscriptions are entered for the calendar year, January-December.

Correspondence inquiries regarding IARS member subscriptions should be sent to the IARS at the Cleveland, Ohio address above. Correspondence regarding all other subscriptions should be sent to Elsevier.

Advertising inquiries should be addressed to: Pharmaceutical Media, Inc, 130 Madison Avenue, New York, NY 10016. The appearance of advertising in publications of the International Anesthesia Research Society does not constitute a guarantee or endorsement of the quality or value of such product or of the claims made for it by its manufacturer. Discussions, views, and recommendations as to medical procedures, choice of drugs, and drug dosages are the responsibility of the authors. Every effort has been made to ensure the accuracy of the information. The editor, publisher, or the Society, however, must disclaim any responsibility or liability. Readers are advised to check package insert information for each drug before administration.

See classified ads section for submission of classified material.

Single issues: Single copy information available from Elsevier Science Publishing Co, Inc, upon request. Back volume (all issues prior to 1983) information available from IARS.

INTERNATIONAL ANESTHESIA RESEARCH SOCIETY

61st CONGRESS - MARCH 14-18, 1987

Buena Vista Palace Hotel, Lake Buena Vista (Orlando), Florida

PRELIMINARY MEETING INFORMATION

PROGRAM / REGISTRATION / HOTEL INFORMATION: Will be mailed in mid-December to all IARS members. (IARS members outside of North America who plan to attend the meeting can receive this material by airmail upon request.) Non-IARS members should request information from the Cleveland Office: 3645 Warrensville Center Road, Cleveland, Ohio 44122. Telephone: (216) 295-1124.

MEETING SCHEDULE: **Registration:** Saturday, March 14, 1-6 pm (continues daily)
Scientific Program: Sunday, March 15 through Wednesday, March 18
Exhibits: Sunday, March 15 through Tuesday, March 17

SCIENTIFIC PROGRAM

T.H. Seldon Distinguished Lecture:
John W. Severinghaus, MD—"The History of Oximetry"

REVIEW COURSE LECTURES:

Jeffrey L. Apfelbaum, MD
Paul G. Barash, MD
Frederic A. Berry Jr, MD
D. Ryan Cook, MD
Benjamin G. Covino, MD
Edmond I. Eger II, MD
Mieczyslaw Finster, MD
Betty L. Grundy, MD

Patricia A. Kapur, MD
Richard S. Matteo, MD
Richard L. McCammon, MD
Edward D. Miller Jr, MD
Ronald D. Miller, MD
Walter S. Nimmo, MD
Donald S. Prough, MD
J. Gerald Reeves, MD
Michael F. Roizen, MD

Paul N. Samuelson, MD
John J. Savarese, MD
Petter A. Steen, MD
Stephen J. Thomas, MD
John H. Tinker, MD
Robert W. Vaughan, MD
Richard B. Weiskopf, MD
Paul F. White, MD

PANEL: *Standards of Care*

Frederick W. Cheney, MD
John H. Eichhorn, MD
Burton S. Epstein, MD
William K. Hamilton, MD
Bruce F. Cullen, MD

PANEL: *Anesthesia Equipment*

John H. Andrews, MD
Forrest W. Fox, MSEE
Betty L. Grundy, MD
A. William Paulsen, PhD
John T. Martin, MD

136 Scientific Papers...55 Scientific Posters...Scientific Exhibits...Theme Luncheons
Board Examinations in Anesthesiology: American Board of Anesthesiology Panel Discussion
Technical (Commercial) Exhibits - Product Seminars: Exhibitor-sponsored morning briefings

REGISTRATION • CME CREDIT • AIR TRAVEL • HOTELS

FEES: IARS Members	\$175 (\$200 on site)
IARS Educational Members	NO FEE
Non-Members	\$350 (\$400 on site)
Non-Member Residents	\$50 (with certifying letter)

CME CREDIT: ACCME/AMA: Category 1-31 hours

SPECIAL AIR FARES: United and Delta Airlines, in cooperation with the IARS, will provide reduced rates for round-trip travel to Orlando. Full details will be included in the preliminary program mailing or can be obtained by calling the following numbers (8 AM to 8:30 PM EST daily) and referring to IARS meeting and code numbers shown.
Delta: 1-800-241-6760 - File No. P-0095. *UAL:* 1-800-521-4041 - Acct. No. 7015-H

HOTELS: The Buena Vista Palace and the Royal Village co-host hotel are situated in Walt Disney World Village and provide complimentary bus service to the Magic Kingdom and Epcot Center. Discounted 3- or 4-day passes will be available to IARS registrants and guests. Hotel rates are seasonally competitive, and one rate covers from single to quad occupancy.

Anesthesia and Analgesia

Contents

Volume 65, Number 12, December 1986

SCIENTIFIC ARTICLES

- | | | |
|---|---|------|
| Halothane Metabolism in Acyanotic and Cyanotic Patients Undergoing Open Heart Surgery | Roger A. Moore, Kathleen W. McNicholas, John D. Gallagher, A. Jay Gandolfi, I. Glenn Sipes, Deanna Kerns, and Donald L. Clark | 1257 |
| Differential Depressant and Electrophysiologic Cardiotoxicity of Local Anesthetics: An Experimental Study with Special Reference to Lidocaine and Bupivacaine | Sherdil Nath, Sören Häggmark, Göran Johansson, and Sebastian Reiz | 1263 |
| Protamine: Does It Alter Right Ventricular Function? | Roberta L. Hines and Paul G. Barash | 1271 |
| Pulmonary Surfactant Films Affected by Solvent Vapors | Goran Enhorning, Ralph Pototschnik, Fred Possmayer, and Rosmarie Burgoyne | 1275 |
| Epidural Anesthesia with Lidocaine and Bupivacaine: Effects of Epinephrine on the Plasma Concentration Profiles | Anton G. L. Burm, Jack W. van Kleef, Marina P. R. R. Gladines, Geert Olthof, and Johan Spierdijk | 1281 |
| Comparison of the Effects of Atropine and Glycopyrrolate on Pulmonary Mechanics in Patients Undergoing Fiberoptic Bronchoscopy | Jonathan R. Thorburn, Michael F. M. James, Charles Feldman, Donald G. Moyes, and Pierre S. Du Toit | 1285 |
| Epinephrine Reduces Systemic Absorption of Extradural Diacetylmorphine | M. A. Jamous, C. W. Hand, R. A. Moore, P. J. Teddy, and H. J. McQuay | 1290 |
| Priming with Atracurium: Improving Intubating Conditions with Additional Doses of Thiopental | Mohamed Naguib, Mohamed Abdulatif, H. K. Gyasi, and G. H. Absood | 1295 |
| Acetaldehyde Syndrome after Celiac Plexus Alcohol Block | Junko Noda, Shinichiro Umeda, Kenjiro Mori, Tatsushige Fukunaga, and Yasuhiko Mizoi | 1300 |
| Evaluation of the Toxicity of Subarachnoid Clonidine, Guanfacine, and a Substance P-Antagonist on Rat Spinal Cord and Nerve Roots: Light and Electron Microscopic Observations after Chronic Intrathecal Administration | Torsten Gordh Jr, Claes Post, and Yngve Olsson | 1303 |
| Effect of Epidural Clonidine on Spinal Cord Blood Flow and Regional and Central Hemodynamics in Pigs | Torsten Gordh Jr, Ulla Feuk, and Karin Norlén | 1312 |
| Pharmacokinetics and Pharmacodynamics of Vecuronium and Pancuronium in Anesthetized Children | Claude Meistelman, Sandor Agoston, Ursula W. Kersten, Claude Saint-Maurice, Anton F. Bencini, and Jean-Pierre Loose | 1319 |

SCIENTIFIC ARTICLES—continued

Retrobulbar Anesthesia: The Role of Hyaluronidase	<i>J. Martin V. Nicoll, Beatrix Treuren, P. Arun Acharya, Kjell Ahlen, and Michael James</i>	1324
Changes in Heart Rate and Rhythm after Intramuscular Succinylcholine with or without Atropine in Anesthetized Children	<i>Raafat S. Hannallah, Tae H. Oh, Willis A. McGill, and Burton S. Epstein</i>	1329
Pulse Oximetry and Circulatory Kinetics Associated with Pulse Volume Amplitude Measured by Photoelectric Plethysmography	<i>Jong-Min Kim, Kasumi Arakawa, Kirk T. Benson, and Deanna K. Fox</i>	1333
Cardiovascular and Neuromuscular Responses to High-dose Pancuronium–Metocurine in Pediatric Burned and Reconstructive Patients	<i>Judy Hagen, Jeevendra Martyn, S. K. Szyfelbein, and Nishan G. Goudsouzian</i>	1340

REVIEW ARTICLE

Electroconvulsive Therapy and Anesthetic Considerations	<i>George Y. Gaines III and D. Ian Rees</i>	1345
---	---	------

CLINICAL REPORTS

Intrathecal Morphine in a Parturient with Cystic Fibrosis	<i>Nicholas H. Hyde and Deborah M. Harrison</i>	1357
A Foam Cuff Endotracheal Tube T-Piece System for Use with Nitrous Oxide Anesthesia	<i>Scott J. Greene, Roy D. Cane, and Barry A. Shapiro</i>	1359
Glass Particle Contamination in Single-Dose Ampules	<i>Karen B. Carbone-Traber and Colin A. Shanks</i>	1361

LETTERS TO THE EDITOR

A Visual Warning Device for Improved Safety	<i>Lynn Williams, Charles Barton, John R. McVey, and Jan D. Smith</i>	1364
Unusual Corrugated Tubing Leak	<i>Thomas J. Poulton</i>	1365
Induction of Anesthesia with Isoflurane in Children	<i>W. S. Wren and A. J. McShane</i>	1365
In Response	<i>Harry G. G. Kingston</i>	1366
A New Device to Smooth Pediatric Inhalation Induction	<i>Art Smerling and Ellise Delphin</i>	1366
On the Use of Priming with Vecuronium for Rapid Sequence Induction	<i>Mitchel Sosis</i>	1367
Comments on the Review of Manual of Pediatric Anesthesia	<i>David J. Steward</i>	1368
Preponderance of Hydrolysis in Inactivation of Atracurium: Questions Remain	<i>Vladimir Nigrovic</i>	1368

LETTERS TO THE EDITOR—*continued*

Variability of Fentanyl Pharmacokinetics in Neonates	R. J. Hudson	136
In Response	John Rodman and Douglas E. Koehnert	137

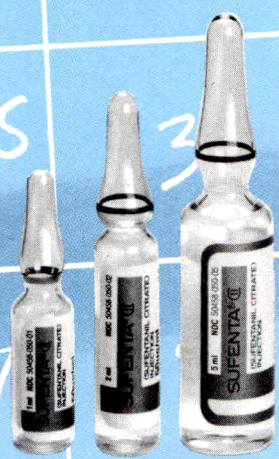
BOOK REVIEWS

Molecular and Cellular Mechanisms of Anesthetics. Sheldon H. Roth and Keith W. Miller, eds.	Gerald A. Gronert	137
Invasive Procedures in Critical Care. Charles L. Sprung and Ake Grenvik, eds.	Douglas B. Coursin	137
Basic Physics and Measurement in Anesthesia (second edition). G. D. Parbrook, P. D. Davis, and E. O. Parbrook.	Kevin K. Tremper and Steven J. Barker	137
Isoflurane (Forane): A Compendium and Reference (second edition). Edmond I. Eger II.	Judith B. Dillman	137
Legal Issues in Transfusion Therapy: Managing Risks in a Changing Environment. Gilbert M. Clark, ed.	William H. L. Dornette	137
Anesthesia in Obstetrics: Maternal, Fetal, and Neonatal Aspects. G. A. Albright, J. E. Fergeson II, and T. H. Joyce III, eds.	Hilda Pedersen	137
Guest Reviewers for 1986		137
Annual Index		137
Author Index		137
Subject Index		137

PATIENT	O.R.	SERVICE	TIME
O'Leary	1	CV	7:45
oskowitz	2	Gen	7:30
Tennings	3	Gen	8:15
Traviotti	4	Gen	7:45
Miller	5	GI	8:00
Foley	6	Gen	9:00

SUFENTA[®]

(sufentanil citrate) Injection 



anesthesia
for longer,
more stressful
procedures

Available in 1 ml, 2 ml, 5 ml ampoules; boxes of ten

Before prescribing, please consult complete prescribing information, of which the following is a brief summary.

CAUTION: Federal Law Prohibits Dispensing Without Prescription.

DESCRIPTION: SUFENTA is a sterile, preservative free, aqueous solution containing sufentanil citrate equivalent to 50 µg per ml of sufentanil base for intravenous injection. The solution has a pH range of 3.5-6.0.

INDICATIONS AND USAGE: SUFENTA (sufentanil citrate) is indicated: As an analgesic adjunct in the maintenance of balanced general anesthesia. As a primary anesthetic agent for the induction and maintenance of anesthesia with 100% oxygen in patients undergoing major surgical procedures, such as cardiovascular surgery or neurosurgical procedures in the sitting position, to provide favorable myocardial and cerebral oxygen balance or when extended postoperative ventilation is anticipated. SEE DOSAGE CHART FOR MORE COMPLETE INFORMATION ON THE USE OF SUFENTA.

CONTRAINDICATIONS: SUFENTA is contraindicated in patients with known hypersensitivity to the drug.

WARNINGS: SUFENTA should be administered only by persons specifically trained in the use of intravenous anesthetics and management of the respiratory effects of potent opioids.

An opioid antagonist, resuscitative and intubation equipment and oxygen should be readily available.

SUFENTA may cause skeletal muscle rigidity, particularly of the truncal muscles. The incidence and severity of muscle rigidity is dose related. Administration of SUFENTA may produce muscular rigidity with a more rapid onset than that seen with fentanyl. SUFENTA may produce muscular rigidity that involves the skeletal muscles of the neck and extremities. The incidence can be reduced by: 1) administration of up to 1/4 of the full paralyzing dose of a non-depolarizing neuromuscular blocking agent just prior to administration of SUFENTA at dosages of up to 8 µg/kg, 2) administration of a full paralyzing dose of a neuromuscular blocking agent following loss of consciousness when SUFENTA is used in anesthetic dosages (above 8 µg/kg) titrated by slow intravenous infusion, or, 3) simultaneous administration of SUFENTA and a full paralyzing dose of a neuromuscular blocking agent when SUFENTA is used in rapidly administered anesthetic dosages (above 8 µg/kg). The neuromuscular blocking agent should be compatible with the patient's cardiovascular status. Adequate facilities should be available for postoperative monitoring and

ventilation of patients administered SUFENTA. It is essential that these facilities be fully equipped to handle all degrees of respiratory depression.

PRECAUTIONS: General: The initial dose of SUFENTA should be appropriately reduced in elderly and debilitated patients. The effect of the initial dose should be considered in determining supplemental doses. Vital signs should be monitored routinely. Nitrous oxide may produce cardiovascular depression when given with high doses of SUFENTA (see CLINICAL PHARMACOLOGY). The hemodynamic effects of a particular muscle relaxant and the degree of skeletal muscle relaxation required should be considered in the selection of a neuromuscular blocking agent. High doses of pancuronium may produce increases in heart rate during SUFENTA-oxygen anesthesia. Bradycardia has been reported infrequently with SUFENTA-oxygen anesthesia and has been responsive to atropine. Respiratory depression caused by opioid analgesics can be reversed by opioid antagonists such as naloxone. Because the duration of respiratory depression produced by SUFENTA may last longer than the duration of the opioid antagonist action, appropriate surveillance should be maintained. As with all potent opioids, profound analgesia is accompanied by respiratory depression and diminished sensitivity to CO₂ stimulation which may persist into or recur in the postoperative period. Appropriate postoperative monitoring should be employed to ensure that adequate spontaneous breathing is established and maintained prior to discharging the patient from the recovery area. Interaction with Other Central Nervous System Depressants: Both the magnitude and duration of central nervous system and cardiovascular effects may be enhanced when SUFENTA is administered to patients receiving barbiturates, tranquilizers, other opioids, general anesthetics or other CNS depressants. In such cases of combined treatment, the dose of one or both agents should be reduced. Head Injuries: SUFENTA may obscure the clinical course of patients with head injuries. Impaired Respiration: SUFENTA should be used with caution in patients with pulmonary disease, decreased respiratory reserve or potentially compromised respiration. In such patients, opioids may additionally decrease respiratory drive and increase airway resistance. During anesthesia, this can be managed by assisted or controlled respiration. Impaired Hepatic or Renal Function: In patients with liver or kidney dysfunction, SUFENTA should be administered with caution due to the importance of these organs in the metabolism and excretion of SUFENTA.

Carcinogenesis, Mutagenesis and Impairment of Fertility: No long-term animal studies of SUFENTA have been performed to evaluate carcinogenic potential. The micronucleus test in female rats revealed that single intravenous

OPERATION	ANESTHESIOLOGIST	SURGEON
Coronary Bypass	Craig/Alvarez	Hodman
Intracranial Aneurysm	Lefcourt/Davis	D'Andrea
Total Hysterectomy	Sanford/Dewey	Higginson
LT. Total Hip Replacement	Connell/Schwartz	Bennett
Anterior Resection of Sigmoid Colon	Cohen/Rothman	Sydney
Thyroidectomy	Jane/Collins	Labadie

doses of SUFENTA as high as 80 µg/kg (approximately 2.5 times the upper human dose) produced no structural chromosome mutations. The Ames *Salmonella typhimurium* metabolic activating test also revealed no mutagenic activity. See ANIMAL TOXICOLOGY for reproduction studies in rats and rabbits.

Pregnancy Category C: SUFENTA has been shown to have an embryocidal effect in rats and rabbits when given in doses 2.5 times the upper human dose for a period of 10 days to over 30 days. These effects were most probably due to maternal toxicity (decreased food consumption with increased mortality) following prolonged administration of the drug. No evidence of teratogenic effects have been observed after administration of SUFENTA in rats or rabbits. There are no adequate and well-controlled studies in pregnant women. SUFENTA should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Labor and Delivery: There are insufficient data to support the use of SUFENTA in labor and delivery. Therefore, such use is not recommended.

Nursing Mothers: It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when SUFENTA is administered to a nursing woman.

Pediatric Use: The safety and efficacy of SUFENTA in children under two years of age undergoing cardiovascular surgery has been documented in a limited number of cases.

Animal Toxicology: The intravenous LD₅₀ of SUFENTA is 16.8 to 18.0 mg/kg in mice, 11.8 to 13.0 mg/kg in guinea pigs and 10.1 to 19.5 mg/kg in dogs. Reproduction studies performed in rats and rabbits given doses of up to 2.5 times the upper human dose for a period of 10 to over 30 days revealed high maternal mortality rates due to decreased food consumption and anoxia, which preclude any meaningful interpretation of the results.

ADVERSE REACTIONS: The most common adverse reactions of opioids are respiratory depression and skeletal muscle rigidity. See CLINICAL PHARMACOLOGY, WARNINGS and PRECAUTIONS on the management of respiratory depression and skeletal muscle rigidity. The most frequent adverse reactions in clinical trials involving 320 patients administered SUFENTA were: hypotension (7%), hypertension (3%), chest wall rigidity (3%) and bradycardia (3%). Other adverse reactions with a reported incidence of less than 1% were: Cardiovascular: tachycardia, arrhythmia; Gastrointestinal: nausea, vomiting; Respiratory: apnea, postoperative respiratory depression, bronchospasm; Dermal:

toxicological: itching, erythema; Central Nervous System: chills; Miscellaneous: intraoperative muscle movement.

DRUG ABUSE AND DEPENDENCE: SUFENTA (sufentanil citrate) is a Schedule II controlled drug substance that can produce drug dependence of the morphine type and therefore has the potential for being abused.

OVERDOSAGE: Overdosage would be manifested by an extension of the pharmacological actions of SUFENTA (see CLINICAL PHARMACOLOGY) as with other potent opioid analgesics. However, no experiences of overdosage with SUFENTA have been established during clinical trials. The intravenous LD₅₀ of SUFENTA in male rats is 9.34 to 12.5 mg/kg (see ANIMAL TOXICOLOGY for LD₅₀s in other species). Intravenous administration of an opioid antagonist such as naloxone should be employed as a specific antidote to manage respiratory depression. The duration of respiratory depression following overdosage with SUFENTA may be longer than the duration of action of the opioid antagonist. Administration of an opioid antagonist should not preclude more immediate countermeasures. In the event of overdosage, oxygen should be administered and ventilation assisted or controlled as indicated for hypoventilation or apnea. A patent airway must be maintained, and a nasopharyngeal airway or endotracheal tube may be indicated. If depressed respiration is associated with muscular rigidity, a neuromuscular blocking agent may be required to facilitate assisted or controlled respiration. Intravenous fluids and vasopressors for the treatment of hypotension and other supportive measures may be employed.

DOSAGE AND ADMINISTRATION: The dosage of SUFENTA should be individualized in each case according to body weight, physical status, underlying pathological condition, use of other drugs, and type of surgical procedure and anesthesia. In obese patients (more than 20% above ideal total body weight), the dosage of SUFENTA should be determined on the basis of lean body weight. Dosage should be reduced in elderly and debilitated patients (see PRECAUTIONS).

world leader in anesthesia research



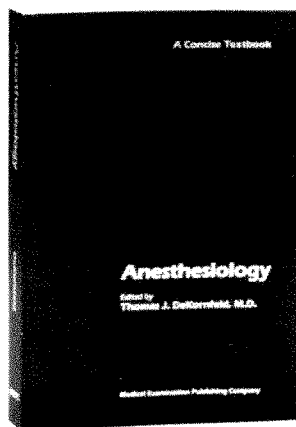
JANISSEN
PHARMACEUTICALS

Janissen Pharmaceutica Inc.
Piscataway, NJ 08854

© Janissen Pharmaceutica Inc. 1986

U.S. Patent No. 3,998,834
7618504-M
January 1986, March 1986

JPI-698



ANESTHESIOLOGY: A CONCISE TEXTBOOK

Edited by **Thomas J. DeKornfeld, M.D.**

Professor of Anesthesiology
Professor of Postgraduate Medicine
and Health Professions Education
Department of Anesthesiology
University of Michigan, Ann Arbor

Here in one volume, twenty-five experts in anesthesiology combine their knowledge in one readable authoritative source. Clinicians will find, in an easily accessible format, a complete and current overview of the clinical applications of anesthesiology as well as the underlying theory. Five major sections detail the practice of anesthesiology; anesthesia and the surgical specialties; anesthesia and systemic problems; anesthesiology as a specialty; and tables and formulas. Discussing areas not usually covered in standard texts, such as legal considerations, ethical questions, and economic aspects of anesthesiology, this book makes an excellent quick reference for the practicing anesthesiologist.

1986

576 pages

0-444-01010-6

paper

\$33.95

CONTENTS

PART I THE SPECIALTY OF ANESTHESIOLOGY

History of Anesthesiology
Education in Anesthesiology
Ethical Questions in the Clinical Practice of Anesthesiology
Legal Considerations in Anesthesiology
Economic Aspects of Anesthesiology
Practice Patterns in Anesthesiology
Nurse Anesthesia and the Anesthesia Care Team

PART II THE PRACTICE OF ANESTHESIOLOGY

Theories of Narcosis
Patient Assessment — Preoperative Visit
Anesthetic Techniques
The Pharmacology of Drugs Used in Anesthesiology

Monitoring Under Anesthesia
Computers and Anesthesia
Respiratory Care
The Recovery Room

PART III ANESTHESIA FOR THE SURGICAL SPECIALTIES

Anesthesia for General Surgery
Anesthesia for Thoracic Surgery
One-Lung Anesthesia
Anesthesia for Cardiac Surgery
Anesthesia for Vascular Surgery
Anesthesia for Orthopedic Surgery
Anesthesia for Urologic Surgery
Anesthesia for Head and Neck Surgery
Anesthesia for Ophthalmic Surgery
Anesthesia for Neurosurgery
Anesthesia for Gynecologic Surgery
Anesthesia for Obstetrics
Anesthesia for Pediatric Surgery

PART IV ANESTHESIA ON THE BASIS OF PATIENT PROBLEMS

The Patient with a Difficult Airway
The Patient with Ischemic Heart Disease Undergoing Noncardiac Surgery
The Patient with Pulmonary Disease
The Patient with Kidney Disease
The Patient with Gastrointestinal and Liver Disease
The Patient with Metabolic Disease
The Patient with Trauma
The Patient with Fluid Imbalance
The Patient with Chronic Pain

PART V MISCELLANEOUS

Reading the Scientific Literature
Equations, Formulas, and Physical Characteristics
Normal Laboratory Values

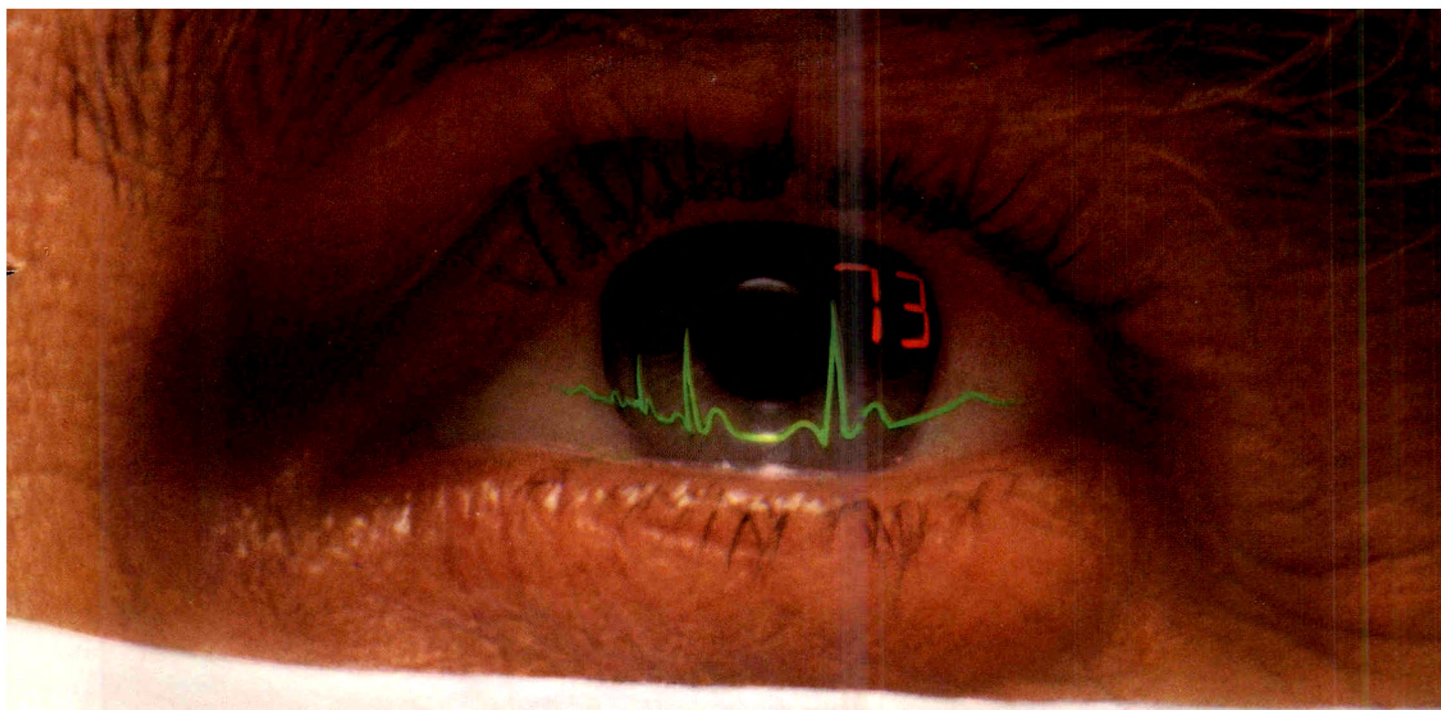
INDEX

Order from your usual supplier or:

MEPC/A division of Elsevier • P.O. Box 1663, Grand Central Station • New York, New York 10163-1663

Note: Price subject to change without notice.

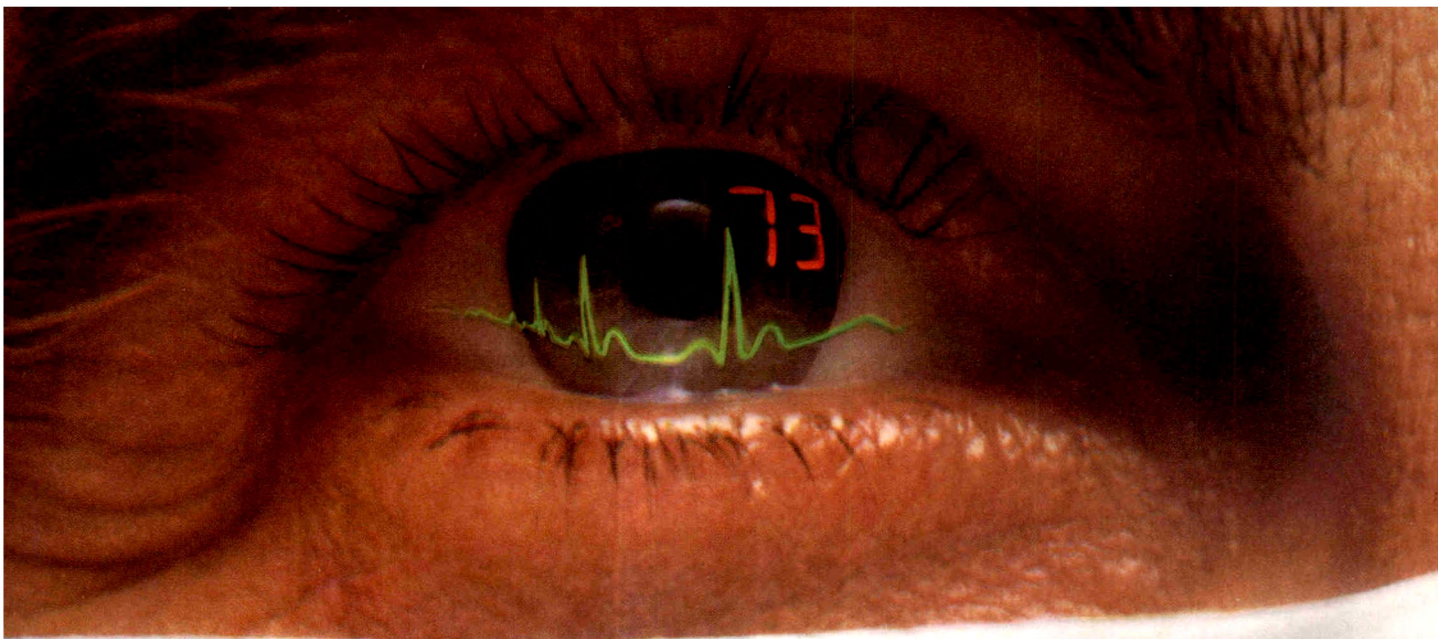
Medical Examination Publishing Company is a division of Elsevier Science Publishing Company, Inc., New York, NY.



See for yourself.

**The only surgical muscle relaxant
free of clinically significant
cardiovascular and histamine-
related side effects...**

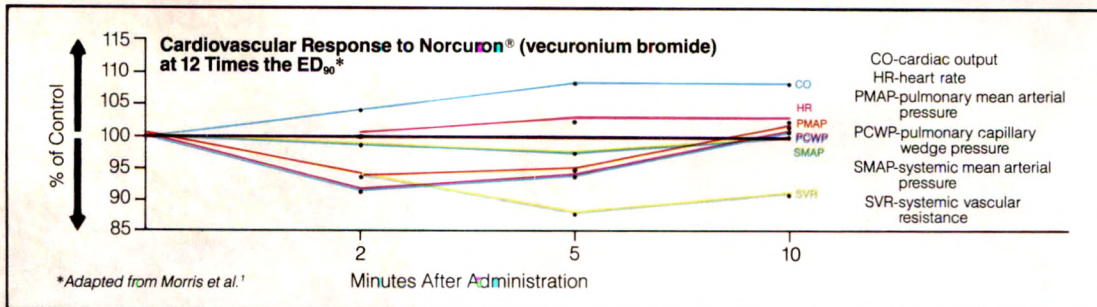
**ideal for your patients, including
those at risk.¹⁻⁵**



See the safety for yourself.

Free of clinically significant cardiovascular effects.*

NORCURON® is the only surgical muscle relaxant for which no clinically significant cardiovascular effects were observed in clinical trials.¹⁻⁴ In fact, even at 12 times effective doses, under halothane anesthesia,¹ NORCURON® produced no tachycardia, hypotension, or abnormalities of cardiodynamic function.

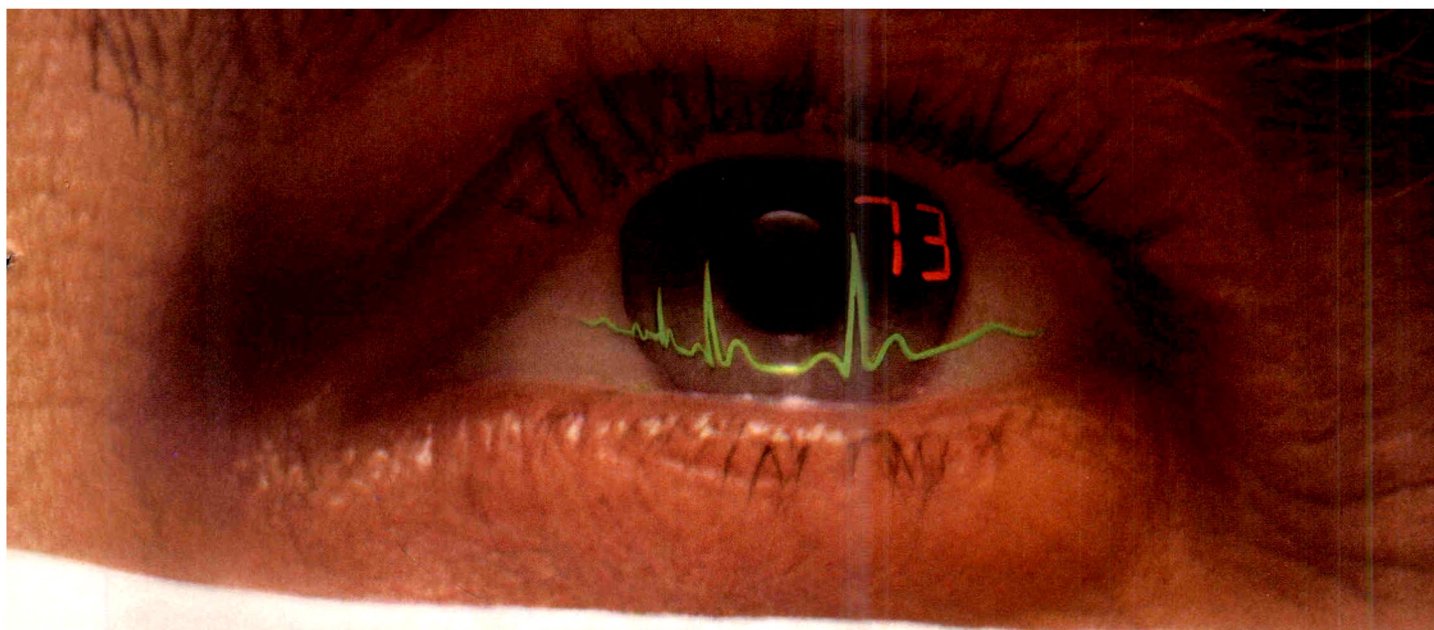


Histamine release or histamine-related side effects unlikely to occur...even at 3.5 times the ED₉₅.⁵

NORCURON® has not been shown to significantly affect circulating histamine, mean arterial blood pressure, and heart rate even in doses at the upper extreme of the recommended clinical range.⁵

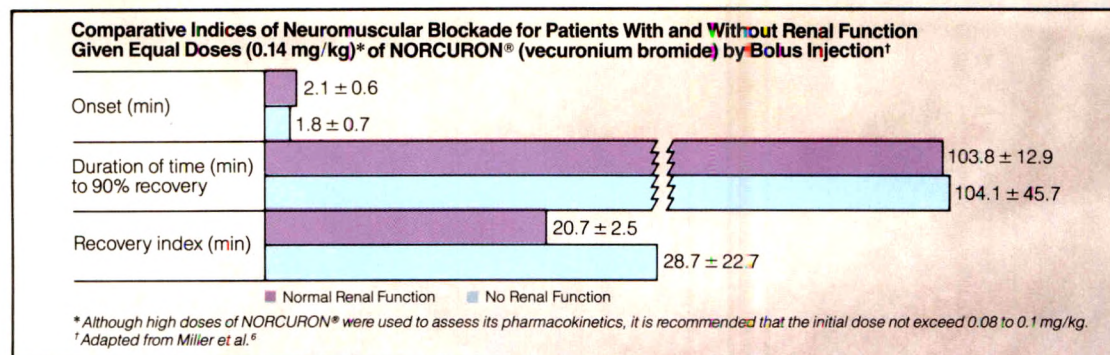
The Effect of Nondepolarizing Muscle Relaxants*				Percent of Control		
Drug	Dose (mg/kg)	xED ₉₅	Histamine	Mean Arterial Pressure	Heart Rate	
Tubocurarine	0.5	1	410	78	116	
Metocurine	0.5†	2	212	79	119	
Atracurium	0.6†	3	192	80	108	
Vecuronium	0.1	1.7	117	100	99	
Vecuronium	0.2	3.5	87	99	102	

*Adapted from Basta et al.⁵
†0.1 mg/kg higher than recommended dose.



Performance unaffected by renal function.⁶

Despite administration of high doses of NORCURON®, no significant differences in onset time, duration of action, or recovery index have been noted between patients with and without renal function.⁶



**The surgical muscle relaxant
ideal for virtually all patients
including those at risk.**

Norcuron®

(vecuronium bromide) injection

See full prescribing information on following page.

References: 1. Morris RB, et al: The cardiovascular effects of vecuronium (ORG NC 45) and pancuronium in patients undergoing coronary artery bypass grafting. *Anesthesiology* 1983; 58:438-440. 2. Durant NN: Norcuron®—a new nondepolarizing neuromuscular blocking agent. *Semin Anesth* 1982; 1:47-56. 3. Krieg N, Crul JF, Booi LH: Relative potency of ORG NC 45, pancuronium, alcuronium, and tubocurarine in anesthetized man. *Br J Anaesth* 1980; 52:783-787. 4. Gallo JA, et al: Hemodynamic effects of bolus injection of

vecuronium in cardiac surgical patients. *Anesthesiology* 1984; 61:A63. 5. Basta SJ, et al: Vecuronium does not alter serum histamine within the clinical dose range. *Anesthesiology* 1983; 59:A273. 6. Miller RD, et al: Pharmacokinetics of vecuronium in patients with kidney disease, in Agoston S, et al (eds). *Clinical Experiences with Norcuron (ORG NC 45, Vecuronium Bromide)*. Amsterdam, Excerpta Medica, 1983, p 124.

Norcuron[®] (vecuronium bromide) injection

THIS DRUG SHOULD BE ADMINISTERED BY ADEQUATELY TRAINED INDIVIDUALS FAMILIAR WITH ITS ACTIONS, CHARACTERISTICS, AND HAZARDS.

DESCRIPTION: NORCURON[®] (vecuronium bromide) injection is a nondepolarizing neuromuscular blocking agent of intermediate duration, chemically designated as piperidinium, 1-(2S, 3a, 5a, 16b, 17b)-3, 17-bis(acetoxy)-2-(1-piperidinyl)hexadecan-16-yl-1-methyl-, bromide.

Norcuron[®] is supplied as a sterile nonpyrogenic freeze-dried buffered cake of very fine microscopic crystalline particles for intravenous injection only. Following reconstitution with solvent (water for injection) the resultant solution is isotonic and has a pH of 4. Each 5 ml vial contains 10 mg vecuronium bromide. Each vial also contains citric acid, dibasic sodium phosphate, sodium hydroxide, and/or phosphoric acid to buffer and adjust pH and mannitol to make isotonic. **CLINICAL PHARMACOLOGY:** Norcuron[®] (vecuronium bromide) injection is a nondepolarizing neuromuscular blocking agent possessing all of the characteristic pharmacological actions of this class of drugs (curariform). It acts by competing for cholinergic receptors at the motor end-plate. The antagonism to acetylcholine is inhibited and neuromuscular block is reversed by acetylcholinesterase inhibitors such as neostigmine, edrophonium, and pyridostigmine. Norcuron[®] is about 18 more potent than pancuronium; the duration of neuromuscular blockade produced by Norcuron[®] is shorter than that of pancuronium at initially equipotent doses. The time to onset of paralysis decreases and the duration of maximum effect increases with increasing Norcuron[®] doses. The use of a peripheral nerve stimulator is of benefit in assessing the degree of muscular relaxation.

The ED₅₀ (dose required to produce 50% suppression of the muscle twitch response with balanced anesthesia) has averaged 0.057 mg/kg (0.049 to 0.062 mg/kg in various studies). An initial Norcuron[®] dose of 0.08 to 0.10 mg/kg generally produces first depression of twitch in approximately 1 minute, good or excellent intubation conditions within 2.5 to 3.0 minutes, and maximum neuromuscular blockade within 3 to 5 minutes of injection in most patients. Under balanced anesthesia, the time to recovery to 25% of control (clinical duration) is approximately 25 to 40 minutes after injection and recovery is usually 95% complete approximately 45-65 minutes after injection of intubating dose. The neuromuscular blocking action of Norcuron[®] is slightly enhanced in the presence of potent inhalational anesthetics. If Norcuron[®] is first administered more than 5 minutes after the start of the initiation of enflurane, isoflurane, or halothane, or when steady state has been achieved, the intubating dose of Norcuron[®] may be decreased by approximately 15% (see DOSAGE AND ADMINISTRATION section). Prior administration of succinylcholine may enhance the neuromuscular blocking effect of Norcuron[®] and its duration of action. With succinylcholine as the intubating agent, initial doses of 0.04-0.06 mg/kg of Norcuron[®] will produce complete neuromuscular block with clinical duration of action of 25-30 minutes. If succinylcholine is used prior to Norcuron[®], the administration of Norcuron[®] should be delayed until the patient starts recovering from succinylcholine-induced neuromuscular blockade. The effect of prior use of other nondepolarizing neuromuscular blocking agents on the activity of Norcuron[®] has not been studied (see Drug Interactions).

Repeated administration of maintenance doses of Norcuron[®] has little or no cumulative effect on the duration of neuromuscular blockade. Therefore, repeat doses can be administered at relatively regular intervals with predictable results. After an initial dose of 0.08 to 0.10 mg/kg under balanced anesthesia, the first maintenance dose (suggested maintenance dose is 0.010 to 0.015 mg/kg) is generally required within 25 to 40 minutes; subsequent maintenance doses, if required, may be administered at approximately 12 to 15 minute intervals. Halothane anesthesia increases the clinical duration of the maintenance dose only slightly. Under enflurane a maintenance dose of 0.010 mg/kg is approximately equal to 0.015 mg/kg dose under balanced anesthesia.

The recovery index (time from 25% to 75% recovery) is approximately 15-25 minutes under balanced or halothane anesthesia. When recovery from Norcuron[®] neuromuscular blocking effect begins, it proceeds more rapidly than recovery from pancuronium. Once spontaneous recovery has started, the neuromuscular block produced by Norcuron[®] is readily reversed with various anticholinesterase agents, e.g., pyridostigmine, neostigmine, or edrophonium in conjunction with an anticholinergic agent such as atropine or glycopyrrolate. There have been no reports of reactivation following satisfactory reversal of Norcuron[®] induced neuromuscular blockade; rapid recovery is a finding consistent with its rapid elimination from the body.

Pharmacokinetics: At clinical doses of 0.04-0.10 mg/kg, 60-80% of Norcuron[®] is usually bound to plasma protein. The distribution half-life following a single intravenous dose (range 0.025-0.280 mg/kg) is approximately 4 minutes. Elimination half-life over this same dosage range is approximately 65-75 minutes in healthy surgical patients and in renal failure patients undergoing transplant surgery. In late pregnancy, elimination half-life may be shortened to approximately 35-40 minutes. The volume of distribution at steady state is approximately 300-400 ml/kg; systemic rate of clearance is approximately 3-4.5 ml/minute/kg. In man, urine recovery of Norcuron[®] varies from 3-5% within 24 hours. Data derived from patients requiring insertion of a T-tube in the common bile duct suggests that 25-50% of a total intravenous dose of vecuronium may be excreted in bile within 42 hours. Only unchanged Norcuron[®] (vecuronium bromide) injection has been detected in human plasma following clinical use. One metabolite, 3-deacetyl vecuronium, has been recovered in the urine of some patients in quantities that account for up to 10% of injected dose; 3-deacetyl vecuronium has also been recovered by T-tube in some patients accounting for up to 25% of the injected dose.

This metabolite has been judged by animal screening (dogs and cats) to have 50% or more of the potency of Norcuron[®]; equipotent doses are of approximately the same duration as Norcuron[®] in dogs and cats. Biliary excretion accounts for about half the dose of Norcuron[®] within 7 hours in the anesthetized rat. Circulatory bypass of the liver (cat preparation) prolongs recovery from Norcuron[®]. Limited data derived from patients with cirrhosis or cholestasis suggests that some measurements of recovery may be doubled in such patients. In patients with renal failure, measurements of recovery do not differ significantly from similar measurements in healthy patients.

Studies involving routine hemodynamic monitoring in good risk surgical patients reveal that the administration of Norcuron[®] in doses up to three times that needed to produce clinical relaxation (0.15 mg/kg) did not produce clinically significant changes in systolic, diastolic or mean arterial pressure. The heart rate, under similar monitoring, remained unchanged in some studies and was lowered by a mean of up to 8% in other studies. A large dose of 0.28 mg/kg administered during a period of no stimulation, while patients were being prepared for coronary artery bypass grafting, was not associated with alterations in rate-pressure-product or pulmonary capillary wedge pressure. Systemic vascular resistance was lowered slightly and cardiac output was increased insignificantly. (The drug has not been studied in patients with hemodynamic dysfunction secondary to cardiac valvular disease). Limited clinical experience (3 patients) with use of Norcuron[®] during surgery for pheochromocytoma has shown that administration of this drug is not associated with changes in blood pressure or heart rate.

Unlike other nondepolarizing skeletal muscle relaxants, Norcuron[®] has no clinically significant effects on hemodynamic parameters and does not counteract those hemodynamic changes or known side effects produced by or associated with anesthetic agents.

Preliminary data on histamine assay in 16 patients and available clinical experience in more than 600 patients indicate that hypersensitivity reactions such as bronchospasm, flushing, redness, hypotension, tachycardia, and other reactions commonly associated with histamine release are unlikely to occur.

INDICATIONS AND USAGE: Norcuron[®] is indicated as an adjunct to general anesthesia, to facilitate endotracheal intubation and to provide skeletal muscle relaxation during surgery or mechanical ventilation.

CONTRAINDICATIONS: None known.

WARNINGS: NORCURON[®] SHOULD BE ADMINISTERED IN CAREFULLY ADJUSTED DOSE BY OR UNDER THE SUPERVISION OF EXPERIENCED CLINICIANS WHO ARE FAMILIAR WITH ITS ACTIONS AND THE POSSIBLE COMPLICATIONS THAT MIGHT OCCUR FOLLOWING ITS USE. THE DRUG SHOULD NOT BE ADMINISTERED UNLESS FACILITIES FOR INTUBATION, ARTIFICIAL RESPIRATION, OXYGEN THERAPY AND REVERSAL AGENTS ARE IMMEDIATELY AVAILABLE. THE CLINICIAN MUST BE PREPARED TO ASSIST OR CONTROL RESPIRATION. In patients who are known to have myasthenia gravis or the myasthenic (Eaton-Lambert) syndrome, small doses of Norcuron[®] may have profound effects. In such patients, a peripheral nerve stimulator and use of a small test dose may be of value in monitoring the response to administration of muscle relaxants.

PRECAUTIONS: **Renal Failure:** Norcuron[®] is well-tolerated without clinically significant prolongation of neuromuscular blocking effect in patients with renal failure who have been optimally prepared for surgery by dialysis. Under emergency conditions in anephric patients some prolongation of neuromuscular blockade may occur; therefore, if anephric patients cannot be prepared for non-oliguric surgery, a lower initial dose of Norcuron[®] should be considered. **Altered Circulation Time:** Conditions associated with slower circulation time in cardiovascular disease, old age, edematous states resulting in increased volume of distribution may contribute to a delay in onset time; therefore dosage should not be increased.

Hepatic Disease: Limited experience in patients with cirrhosis or cholestasis has revealed prolonged recovery time in keeping with the role the liver plays in Norcuron[®] metabolism and excretion (see Pharmacokinetics). Data currently available do not permit dosage recommendations in patients with impaired liver function.

UNDER THE ABOVE CONDITIONS, USE OF A PERIPHERAL NERVE STIMULATOR FOR ADEQUATE MONITORING OF NEUROMUSCULAR BLOCKING EFFECT WILL PRECLUDE INADVERTENT EXCESS DOSING.

Severe Obesity or Neuromuscular Disease: Patients with severe obesity or neuromuscular disease may pose airway and/or ventilatory problems requiring special care before, during and after the use of neuromuscular blocking agents such as Norcuron[®].

Malignant Hyperthermia: Many drugs used in anesthetic practice are suspected of being capable of triggering a potentially fatal hypermetabolism of skeletal muscle known as malignant hyperthermia. There are insufficient data derived from screening in susceptible animals (swine) to establish whether or not Norcuron[®] is capable of triggering malignant hyperthermia.

Norcuron[®] has no known effect on consciousness, the pain threshold or cerebellar. Administration must be accompanied by adequate anesthesia.

Drug Interactions: Prior administration of succinylcholine may enhance the neuromuscular blocking effect of Norcuron[®] (vecuronium bromide) injection and its duration of action. If succinylcholine is used before Norcuron[®], the administration of Norcuron[®] should be delayed until the succinylcholine effect shows signs of wearing off. With succinylcholine as the intubating agent, initial doses of 0.04-0.06 mg/kg of Norcuron[®] may be administered to produce complete neuromuscular block with clinical duration of action of 25-30 minutes (see CLINICAL PHARMACOLOGY). The use of Norcuron[®] before succinylcholine, in order to attenuate some of the side effects of succinylcholine, has not been sufficiently studied.

Other nondepolarizing neuromuscular blocking agents (pancuronium, d-tubocurarine, mivacurium, and gallamine) act in the same fashion as does Norcuron[®]; therefore these drugs and Norcuron[®] may manifest an additive effect when used together. There are insufficient data to support concomitant use of Norcuron[®] and other competitive muscle relaxants in the same patient.

Intubating Agent Anesthetics: Use of volatile inhalational anesthetics such as enflurane, isoflurane, and halothane with Norcuron[®] will enhance neuromuscular blockade. Potentiation is most prominent with use of enflurane and isoflurane. With the above agents the initial dose of Norcuron[®] may be the same as with balanced anesthesia unless the inhalational anesthetic has been administered for a sufficient time at a sufficient dose to have reached clinical equilibrium (see CLINICAL PHARMACOLOGY).

Antibiotics: Parenteral/intraperitoneal administration of high doses of certain antibiotics may intensify or produce neuromuscular block on their own. The following antibiotics have been associated with various degrees of paralysis: aminoglycosides (such as neomycin, streptomycin, kanamycin, gentamicin, and dihydrostreptomycin), tetracyclines, bacitracin, polymyxin B, colistin, and sodium colistimethate. If these or other newly introduced antibiotics are used in conjunction with Norcuron[®] during surgery, unexpected prolongation of neuromuscular block should be considered a possibility. **Other:** Experience concerning injection of quinine during recovery from use of other muscle relaxants suggests that recurrent paralysis may occur. This possibility must also be considered for Norcuron[®]. Norcuron[®] induced neuromuscular blockade has been counteracted by alkalosis and enhanced by acidosis in experimental animals (cat). Electrolyte imbalance and diseases which lead to electrolyte imbalance, such as adrenal cortical insufficiency, have been shown to alter neuromuscular blockade. Depending on the nature of the imbalance, either enhancement or inhibition may be expected. Magnesium salts, administered for the management of toxemia of pregnancy, may enhance the neuromuscular blockade.

Drug/Laboratory Test Interactions: None known.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Long-term studies in animals have not been performed to evaluate carcinogenic or mutagenic potential or impairment of fertility.

Pregnancy: Pregnancy Category C: Animal reproduction studies have not been conducted with Norcuron[®]. It is also not known whether Norcuron[®] can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Norcuron[®] should be given to a pregnant woman only if clearly needed.

Pediatric Use: Infants under 1 year of age but older than 7 weeks, also tested under halothane anesthesia, are moderately more sensitive to Norcuron[®] on a mg/kg basis than adults and take about 1½ times as long to recover. Information presently available does not permit recommendations for usage in neonates.

ADVERSE REACTIONS: Norcuron[®] was well-tolerated and produced no adverse reactions during extensive clinical trials. The most frequent adverse reaction to nondepolarizing blocking agents as a class consists of an extension of the drug's pharmacological action beyond the time period needed for surgery and anesthesia. This may vary from skeletal muscle weakness to profound and prolonged skeletal muscle paralysis resulting in respiratory insufficiency or apnea. Inadequate reversal of the neuromuscular blockade, although not yet reported, is possible with Norcuron[®] as with all curariform drugs. These adverse reactions are managed by manual or mechanical ventilation until recovery is judged adequate. Little or no increase in frequency of blockade or duration of action of Norcuron[®] is noted from the use of thiobarbiturates, narcotic analgesics, nitrous oxide, or droperidol. See OVERDOSEAGE for discussion of other drugs used in anesthetic practice which also cause respiratory depression.

OVERDOSEAGE: There has been no experience with Norcuron[®] overdosage. The possibility of isotonic overdosage can be minimized by carefully monitoring muscle twitch response to peripheral nerve stimulation.

Excessive doses of Norcuron[®] can be expected to produce enhanced pharmacological effects. Residual neuromuscular blockade beyond the time period needed for surgery and anesthesia may occur with Norcuron[®] as with other neuromuscular blockers. This may be manifested by skeletal muscle weakness, decreased respiratory reserve, low tidal volume, or apnea. A peripheral nerve stimulator may be used to assess the degree of residual neuromuscular blockade and help to differentiate residual neuromuscular blockade from other causes of decreased respiratory reserve.

Respiratory depression may be due either wholly or in part to other drugs used during the conduct of general anesthesia such as narcotics, thiobarbiturates and other central nervous system depressants. Under such circumstances the primary treatment is maintenance of a patent airway and manual or mechanical ventilation until complete recovery of normal respiration is assured. Reagents (pyridostigmine bromide injection), neostigmine, or edrophonium, in conjunction with atropine or glycopyrrolate will usually antagonize the skeletal muscle relaxant action of Norcuron[®]. Satisfactory reversal can be judged by adequacy of skeletal muscle tone and by adequacy of respiration. A peripheral nerve stimulator may also be used to monitor restoration of twitch height. Failure of prompt reversal (within 30 minutes) may occur in the presence of extreme debilitation, cardiovascular disease, and with concomitant use of certain broad spectrum antibiotics, or anesthetic agents and other drugs which enhance neuromuscular blockade or cause respiratory depression of their own. Under such circumstances the management is the same as that of prolonged neuromuscular blockade. Ventilation must be supported by artificial means until the patient has resumed control of his respiration. Prior to the use of reversal agents, reference should be made to the specific package insert of the reversal agent.

DOSEAGE AND ADMINISTRATION: Norcuron[®] (vecuronium bromide) injection is for intravenous use only. This drug should be administered by or under the supervision of experienced clinicians familiar with the use of neuromuscular blocking agents. Dosage must be individualized in each case. The dosage information which follows is derived from studies based upon units of drug per unit of body weight and is intended to serve as a guide only, especially regarding enhancement of neuromuscular blockade of Norcuron[®] by volatile anesthetics and by prior use of succinylcholine (see PRECAUTIONS/Drug Interactions). Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

To obtain maximum clinical benefits of Norcuron[®] and to minimize the possibility of overdosage, the monitoring of muscle twitch response to peripheral nerve stimulation is advised.

The recommended initial dose of Norcuron[®] is 0.08 to 0.10 mg/kg (1.4 to 1.75 times the ED₅₀) given as an intravenous bolus injection. This dose can be expected to produce good or excellent non-emergent intubation conditions in 2.5 to 3.0 minutes after injection. Under balanced anesthesia, clinically required neuromuscular blockade lasts approximately 25 to 30 minutes, with recovery to 25% of control achieved approximately 25 to 40 minutes after injection and recovery to 95% of control achieved approximately 45-65 minutes after injection. In the presence of potent inhalational anesthetics, the neuromuscular blocking effect of Norcuron[®] is enhanced. If Norcuron[®] is first administered more than 5 minutes after the start of intubation agent or when steady state has been achieved, the initial Norcuron[®] dose may be reduced by approximately 15%, i.e., 0.060 to 0.085 mg/kg.

Prior administration of succinylcholine may enhance the neuromuscular blocking effect and duration of action of Norcuron[®]. If intubation is performed using succinylcholine, a reduction of initial dose of Norcuron[®] to 0.04-0.06 mg/kg with intubation anesthesia and 0.05-0.06 mg/kg with balanced anesthesia may be required.

During prolonged surgical procedures, maintenance doses of 0.010 to 0.015 mg/kg of Norcuron[®] are recommended; after the initial Norcuron[®] injection, the first maintenance dose will generally be required within 25 to 40 minutes. However, clinical criteria should be used to determine the need for maintenance doses. Since Norcuron[®] lacks clinically important cumulative effects, subsequent maintenance doses, if required, may be administered at relatively regular intervals for each patient, ranging approximately from 12 to 15 minutes under balanced anesthesia, slightly longer under intubation agents. (If less frequent administration is desired, higher maintenance doses may be administered.)

Should there be reason for the selection of larger doses in individual patients, initial doses ranging from 0.15 mg/kg up to 0.28 mg/kg have been administered during surgery under halothane anesthesia without ill effects to the cardiovascular system being noted as long as ventilation is properly maintained (see CLINICAL PHARMACOLOGY). **Dosage in Children:** Older children (10 to 17 years of age) have approximately the same dosage requirements (mg/kg) as adults and may be managed the same way. Younger children (1 to 10 years of age) may require a slightly higher initial dose and may also require supplementation slightly more often than adults. Infants under one year of age but older than 7 weeks are moderately more sensitive to Norcuron[®] on a mg/kg basis than adults and take about 1½ times as long to recover. See also subsection of PRECAUTIONS titled Pediatric Use. Information presently available does not permit recommendation on usage in neonates (see PRECAUTIONS).

COMPATIBILITY: Norcuron[®] is compatible in solution with:

0.9% NaCl solution

5% glucose in saline

5% glucose in water

Lactated Ringers

HOW SUPPLIED: 5 ml vials (contains 10 mg of active ingredient) and 5 ml ampul of preservative-free sterile water for injection as the diluent. Boxes of 10 (NDC#0052-0442-17).

5 ml vials (contains 10 mg of active ingredient) only. DILUENT (Sterile Water for Injection, USP) NOT SUPPLIED. Boxes of 10 (NDC#0052-0442-57).

STORAGE: PROTECT FROM LIGHT. Store at 15°-30°C (59°-86°F).

AFTER RECONSTITUTION: Solution may be stored in refrigerator or kept at room temperature not to exceed 30°C (86°F). DISCARD SOLUTION AFTER 24 HOURS. DISCARD UNUSED PORTION. SINGLE USE VIALS. Manufactured by ORGANON INC. by BEN VENUE LABORATORIES, INC., Bedford, OH 44146. ISSUED 5/86



ORGANON INC.
WEST ORANGE, NEW JERSEY 07062

SIEMENS



Servo Gas Monitor 120 for instant control of anesthesia

Fast, accurate and safe monitoring of anesthetic agents. You can clearly read the difference in gas concentration between inspiration and expiration, and see when a steady state has been reached.

- Analogue and digital monitoring of halothane, enflurane and isoflurane concentrations, breath by breath, with alarm.
- Digital O₂-monitoring with alarm.
- Fits most equipment — both rebreathing and non-rebreathing systems.

- No gas loss — no pollution of the operation room.
- Insensitive to humidity.
- Compact and light in weight.

Please contact us for more information.



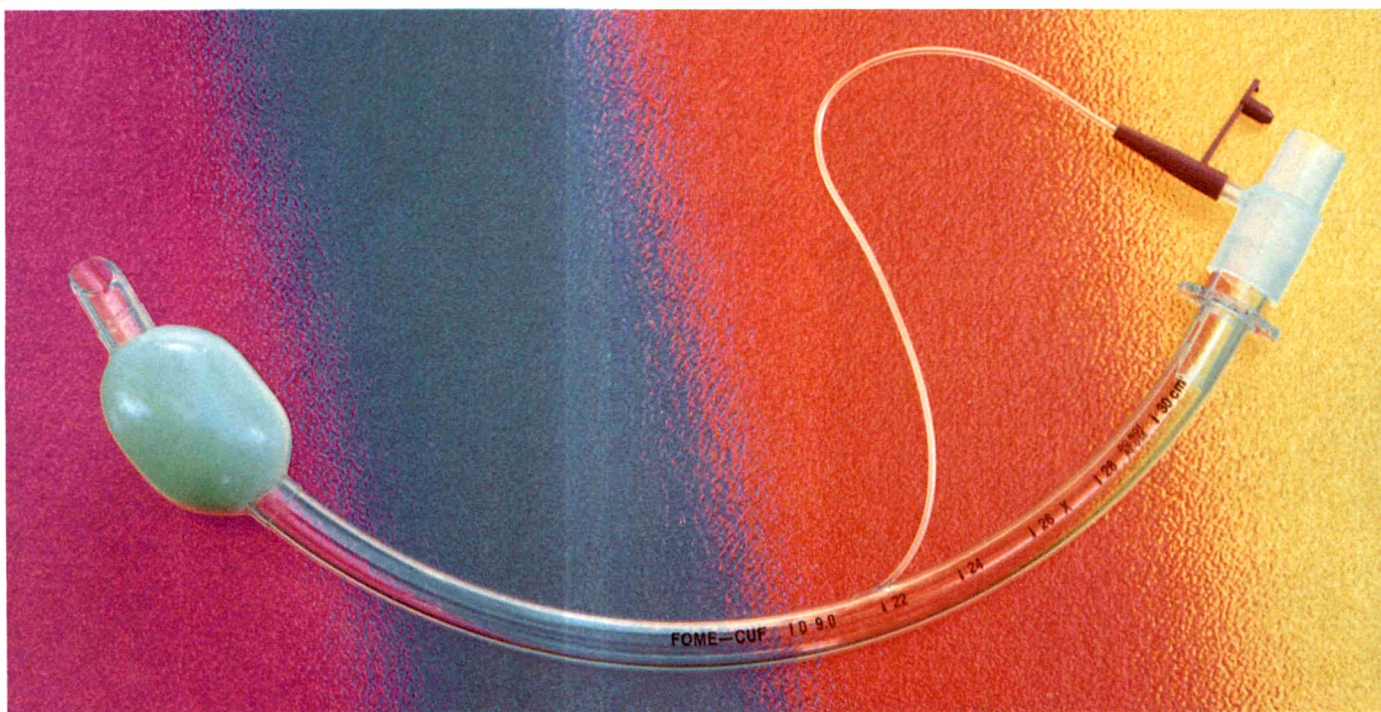
Servo Ventilator Systems

Siemens-Elema Ventilator Systems,
2360 North Palmer Drive, Schaumburg, Illinois 60173-3887.
Tel (800) 323-1281.

For countries outside the U.S.
Siemens-Elema AB, Ventilator Division, S-171 95 Solna, Sweden.

BIVONA INTRODUCES THE PVC FOME-CUF®

With Sideport Airway Connector



The "Intelligent" System

"Intelligent" because the new system automatically equalizes the intracuff pressure and the airway pressure - *no need to monitor cuff pressure.*

"Intelligent" because the new system won't permit nitrous oxide to build up in the cuff during nitrous oxide administration - *no need to bleed the cuff during the course of anesthesia.*

"Intelligent" because the new system automatically adjusts the cuff volume to match the changing tracheal volume - *no danger of tracheal dilatation, even if prolonged mechanical ventilation is required.*

Why not start your next case with Bivona's PVC Fome-Cuf® tube with sideport airway connector and experience the benefits of the "intelligent" system?

Available in sizes 7.0, 7.5, 8.0, 8.5, 9.0 mm I.D.
Packaged individual, Sterile, Single use, disposable
Manufactured under U.S.A. and International Patents

To order or obtain the name of your local dealer contact:

BIVONA INC., 5700 WEST 23RD AVE.
GARY, INDIANA 46406 U.S.A.
219-989-9150
TELEX 27-6107

Halothane Metabolism in Acyanotic and Cyanotic Patients Undergoing Open Heart Surgery

Roger A. Moore, MD, Kathleen W. McNicholas, MD, John D. Gallagher, MD,
A. Jay Gandolfi, PhD, I. Glenn Sipes, PhD, Deanna Kerns, MS, and Donald L. Clark, MD

MOORE RA, McNICHOLAS KW, GALLAGHER JD, GANDOLFI AJ, SIPES IG, KERNS D, CLARK DL. Halothane metabolism in acyanotic and cyanotic patients undergoing open heart surgery. *Anesth Analg* 1986;65:1257-62.

The metabolism of halothane was examined in patients with acyanotic and cyanotic congenital heart disease undergoing open heart surgery. Statistically significant ($P < 0.05$) pre-surgical differences between acyanotic and cyanotic groups included pH (7.46 ± 0.02 vs 7.36 ± 0.02), PaO_2 (277 ± 58 vs 51 ± 3 torr), O_2 saturation (97 ± 1 vs $74 \pm 4\%$), and hematocrit (45 ± 3 vs $58 \pm 2\%$). Serum fluoride levels were significantly greater in cyanotic than in acyanotic groups 2-4 hours after initial exposure to halothane. Both groups had significant intragroup increases in serum levels of fluo-

ride, bromide, and trifluoroacetic acid. Significant increases in serum levels of lactate dehydrogenase, creatinine phosphokinase, and glutamic oxaloacetate transaminase were observed in both groups, whereas, the cyanotic patients had additional significant increases in blood urea nitrogen and direct bilirubin. The cyanotic group also had higher total and direct serum bilirubin levels than the acyanotic group. Therefore, patients with cyanotic congenital heart disease had greater reductive metabolism of halothane than acyanotics. However, cyanotic and acyanotic patients had essentially similar postoperative derangements in hepatic and renal function.

Key Words: ANESTHETICS, VOLATILE—halothane. TOXICITY—halothane. BIOTRANSFORMATION (DRUG)—halothane.

During halothane anesthesia approximately 20% of absorbed halothane is metabolized (1). Under normoxic conditions, metabolism occurs primarily by oxidation with the liberation of bromide and trifluoroacetic acid, and the release of little free fluoride. Under hypoxic conditions metabolism can occur by reductive pathways with liberation of free fluoride and potentially hepatotoxic metabolites (2,3). In animal studies, the combination of hepatic enzyme induction and a hypoxic halothane mixture consistently produces centrilobular hepatic necrosis (3-5). It is not known if the same pathologic findings can be found in humans under similar physiologic conditions.

Halothane continues to be a valuable and frequently used anesthetic. Patients with cyanotic congenital heart disease present the opportunity for ob-

serving whether or not halothane undergoes increased reductive metabolism under relatively hypoxic conditions. In this study we observed the liberation of serum fluoride in cyanotic and acyanotic patients undergoing cardiac surgery during halothane anesthesia. Changes in hepatic and renal serum chemistries in these two groups were also evaluated.

Materials and Methods

After obtaining institutional review board approval and individual informed consent, 20 patients with congenital heart disease scheduled for open heart surgery were entered into the study. Patients were divided into either acyanotic (AC) or cyanotic (C) groups ($n = 10$) based on arterial oxygen saturation obtained at the time of cardiac catheterization. Classification of patients in the AC or C groups was confirmed following induction of anesthesia by the presence of an arterial oxygen saturation greater than or less than 90%, respectively, with an FI_{O_2} of greater than 0.98.

One hour before surgery, all patients were premedicated with scopolamine, 0.01 mg/kg (max 0.4 mg), pentobarbital, 2.0 mg/kg (max 100 mg), and morphine, 0.2 mg/kg (max 10 mg) intramuscularly (IM).

This research sponsored by the Deborah Foundation.

Received from the Departments of Anesthesiology and Cardiovascular Surgery, Deborah Heart and Lung Center, the Department of Anesthesiology, University of Pennsylvania, and the Departments of Anesthesiology, Pharmacology, and Toxicology, University of Arizona. Accepted for publication July 21, 1986.

Address correspondence to Dr. Moore, Department of Anesthesia, Deborah Heart and Lung Center, Trenton Road, Browns Mills, NJ 08015.

On arrival in the operating room patients had intravenous and radial arterial catheters inserted either under premedicant sedation alone or with the addition of 50% nitrous oxide. A baseline sample of blood was obtained through the arterial catheter for determination of serum fluoride (F), bromide (B), and trifluoroacetic acid (TFAA) levels. Patients then received halothane (up to 2% inspired, provided through a calibrated Dräger Halothane Vapor 19 vaporizer) and pancuronium bromide 0.01 mg/kg while nitrous oxide, if used, was discontinued. Halothane served as the sole anesthetic for the remainder of the operative procedure with supplemental doses of pancuronium bromide as necessary. Accurate records of the concentrations and duration of halothane exposure were kept for each patient in order to approximate MAC minutes of halothane exposure. After 15 min of controlled ventilation, baseline arterial blood gas tensions while breathing an FiO_2 greater than 0.98% were obtained. Hypothermic cardiopulmonary bypass was established in all patients, by using a Sci-Med membrane oxygenator. Hypothermic arrest techniques were not used for any patient. Arterial blood gas tensions were also measured 1 hr after discontinuation of cardiopulmonary bypass.

Additional blood samples for measurements of F, B, and TFAA were obtained at 1 hr (before bypass), 2-4 hr (after cardiopulmonary bypass), 8-12 hr, 24 hr, and 48-72 hr after initial halothane exposure. All samples were collected, and serum was separated without exposure to metal or glass. Samples were frozen at -60°C until analysis could be performed. Analysis of F was performed using an Orion fluoride ion specific electrode (2). Serum B and TFAA analyses were performed by previously described gas chromatographic techniques (6). Total urine outputs and total pancuronium doses were recorded at each of the halothane metabolite blood sampling points.

Blood samples were also obtained for measurements of blood urea nitrogen (BUN), creatinine, total bilirubin (BT), direct bilirubin (BD), alkaline phosphatase (AP), serum glutamic oxaloacetate transaminase (SGOT), serum glutamic pyruvate transaminase (SGPT), lactate dehydrogenase (LDH), and creatinine phosphokinase (CPK) on 1) the day prior to surgery, 2) the day of surgery on arrival in the intensive care unit, 3) the second postoperative day, and 4) the fifth postoperative day.

Need for postoperative inotropes, duration of use of inotropes, the first cardiac index measured in the intensive care unit, central venous pressure in the intensive care unit, time to extubation, duration of cardiopulmonary bypass and the operative procedure, and total units of transfused packed red blood cells were recorded for each patient.

Statistical comparisons of the AC and C groups for demographic, hemodynamic, urine output, blood gas tensions, transfusions, and drug exposure data, as well as durations of inotrope use, cardiopulmonary bypass, operative procedure, and intubation were performed using unpaired *t*-tests. Comparison of frequency of inotrope use was performed using the test for significance of difference between two proportions (7). Inter- and intragroup comparisons of halothane metabolites and blood chemistries were performed using the two-way analysis of variance (ANOVA). Determinations of correlation coefficients between data sets were obtained using the Pearson product-moment correlation. Significance was considered to occur at $P < 0.05$. All data are presented as mean \pm SEM.

Results

The congenital defects in patients in the AC group included ventricular septal defect (2), acyanotic tetralogy of Fallot (5), partial anomalous pulmonary venous return (1), and atrioventricular canal (2), whereas, all patients in the C group had cyanotic tetralogy of Fallot. Comparisons of AC and C revealed no significant differences in age (8.0 ± 1.5 vs 11.1 ± 2.8 yr), sex (5 vs 4 females), height (117 ± 8 vs 129 ± 10 cm), weight (23.1 ± 4.7 vs 24.9 ± 3.8 kg), duration of operation (190 ± 12 vs 212 ± 16 min), duration of cardiopulmonary bypass (61 ± 8 vs 74 ± 8 min), or MAC minutes halothane exposure (128 ± 7 vs 131 ± 14 min). Comparisons of AC and C groups for time to extubation (25.1 ± 8.4 vs 49.1 ± 10.7 hr), need for intraoperative inotropes (4 of 10 vs 6 of 10 patients), need for intensive care unit inotropes (5 of 10 vs 9 of 10 patients), postoperative central venous pressures (14.5 ± 1.6 vs 12.4 ± 1.8 torr), total packed red blood cell transfusions (3.1 ± 0.8 vs 3.1 ± 0.8 units) and initial cardiac indices in intensive care unit (3.5 ± 0.5 vs $3.5 \pm 0.3 \text{ L}\cdot\text{min}^{-1}\cdot\text{m}^{-2}$) were not significantly different. However, the tendency for a longer duration of intubation and more frequent use of inotropes in both the operating room and the intensive care unit suggests that the cardiac disease was more severe in group C than in group AC. The significantly shorter duration of inotrope usage in the AC group compared with the C group postoperatively (39.5 ± 17 vs 82.8 ± 13.5 hr) supports this observation.

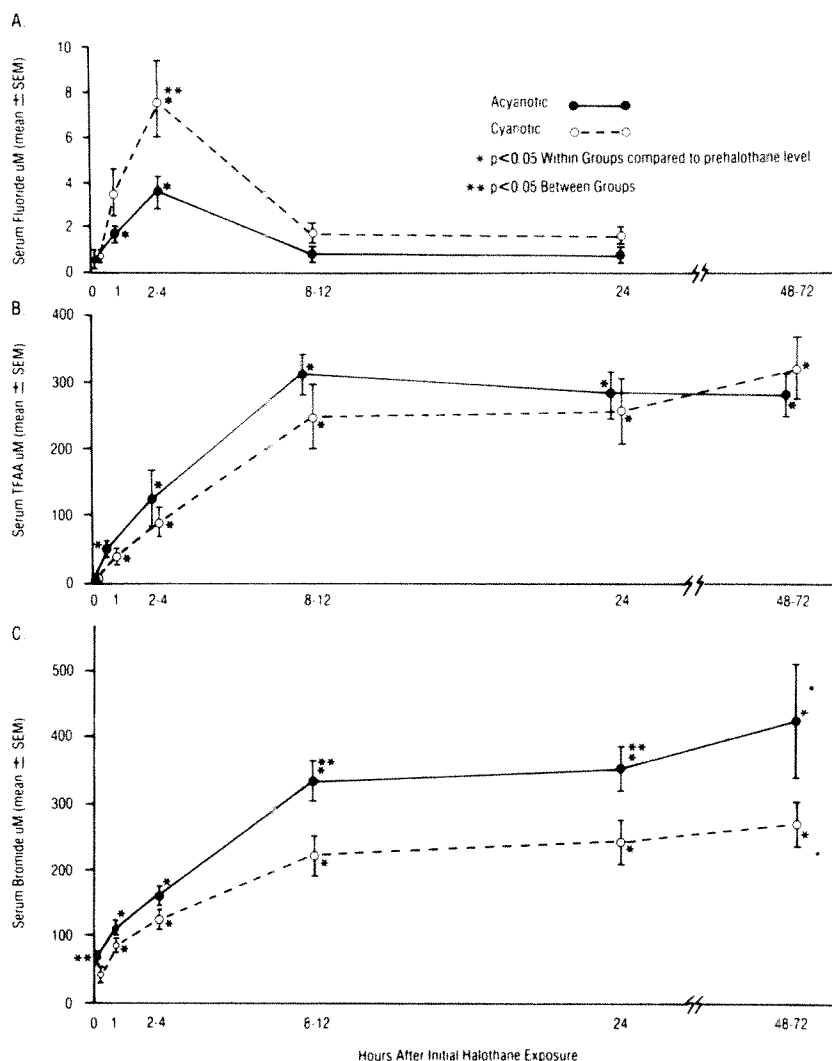
Preoperative hematocrits were significantly higher in the C group than in the AC group. Initial intraoperative blood gas tensions ($\text{FiO}_2 > 0.98$) revealed significantly lower pH, PaO_2 , and O_2 saturations in the C group. Postcardiopulmonary bypass arterial blood gas tensions ($\text{FiO}_2 > 0.98$) showed a significantly lower PaCO_2 in the C group (Table 1).

Table 1. Arterial Blood Gas Data Pre- and Post-Cardiopulmonary Bypass for Acyanotic and Cyanotic Groups

	pH	PaO ₂ (mm Hg)	O ₂ Sat (%)	Paco ₂ (mm Hg)	Base deficit	Hct (%)
Acyanotic prebypass	7.46 ± 0.02	277 ± 58	97 ± 1	32 ± 3	0.66 ± 0.54	45.4 ± 2.6
Cyanotic prebypass	7.36 ± 0.02 ^a	51 ± 03 ^a	74 ± 4 ^a	39 ± 3	1.57 ± 0.44	57.9 ± 1.9 ^a
Acyanotic postbypass	7.42 ± 0.01	406 ± 40	—	36 ± 1	0.01 ± 0.44	32.1 ± 1.2
Cyanotic postbypass	7.45 ± 0.01	484 ± 30	—	30 ± 1	1.83 ± 0.76	31.9 ± 1.4

^aP < 0.05 between group differences.

Figure 1. Serum levels of (A) fluoride, (B) tri-fluoroacetic acid, and (C) bromide in acyanotic and cyanotic groups of patients after exposure to halothane. Significant within-group (*) and between-group (**) differences are indicated.



Comparisons of total urine output (ml/kg) and total pancuronium bromide (mg/kg) from the time of initial halothane exposure at each of the halothane sampling periods did not reveal significant between group differences. A tendency for less total pancuronium dosages in group AC than in group C at the 48 hr (0.43 ± 0.1 vs 0.65 ± 0.2 mg/kg) and 72 hr (0.48 ± 0.16 vs 0.89 ± 0.35 mg/kg) sampling points served as a reflection of the relatively shorter intubation period for these patients.

Halothane Metabolism

The reductive metabolism of halothane, as evidenced by serum F levels, was significantly greater in C compared with AC during the postcardiopulmonary bypass period (2-4 hr). Intragroup evaluation revealed an increase in serum F in group AC during the prebypass period and in both groups during the postcardiopulmonary bypass period (Fig. 1A). Production of TFAA, an indicator of oxidative metabolism of halo-

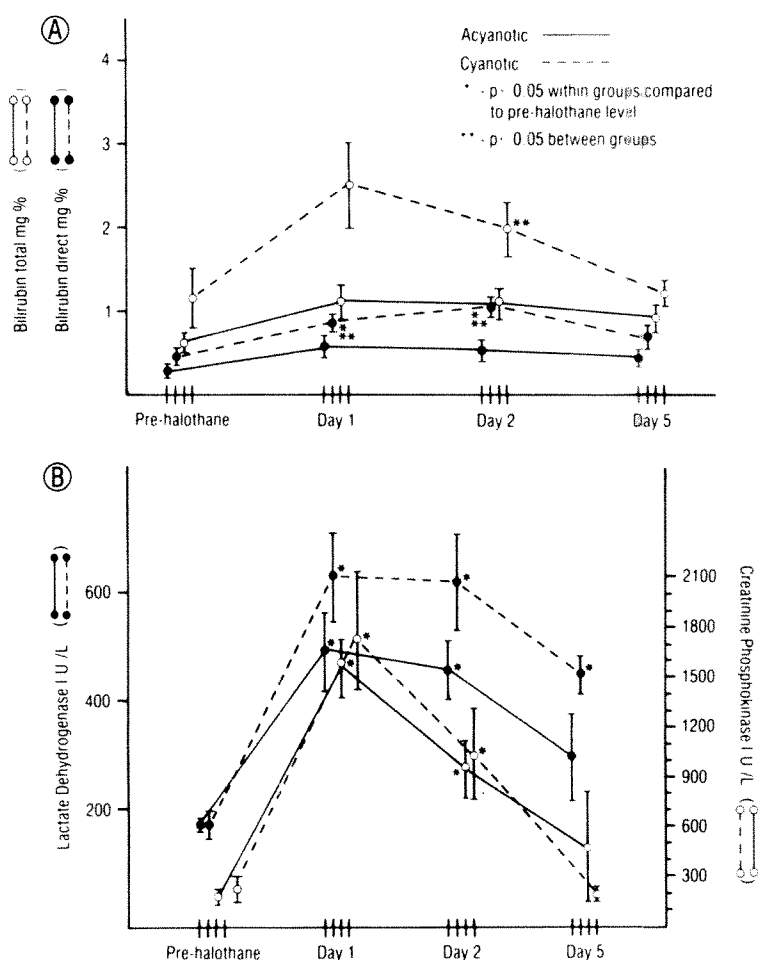


Figure 2. Means with standard error of the mean for (A) serum total and direct bilirubins, and (B) lactate dehydrogenase and serum creatinine phosphokinase in acyanotic and cyanotic groups of patients before and after open heart surgery. Significant within-group (*) and between-group (**) differences are indicated.

thane, was elevated for both groups at all time points after halothane exposure with no significant between-group differences (Fig. 1B). Between-group comparison of serum levels of B revealed significantly higher levels in the AC group before halothane exposure, as well as at the 8–12 and 24-hr sampling periods. Both groups had significantly elevated B at all posthalothane exposures time points (Fig. 1C).

Serum Blood Chemistries

Between-group comparisons of blood chemistries revealed the C group had a significantly higher BD than the AC group following the surgical procedure, whereas, both BD and BT were significantly higher in C on the day after surgery. The intragroup comparisons of BT, BD, SGPT, SGOT, LDH, BUN, and CPK with significant changes are indicated in Figures 2A and 2B, and 3A and 3B. No significant intergroup differences between AC and C were found for AP or for creatinine (Table 2).

Correlation coefficients between peak F levels and

peak blood chemistries for each group were determined with significant r values in the AC group found for creatinine ($r = 0.48$) and in the C group for BD ($r = 0.48$), SGPT ($r = 0.76$), LDH ($r = 0.67$), creatinine ($r = 0.74$), and CPK ($r = 0.57$). Peak BT and BD were not found to have significant correlation coefficients with preoperative hematocrits or duration of cardiopulmonary bypass. Peak F correlated inversely with preoperative oxygen saturation when both AC and C groups were evaluated together ($r = -0.45$).

Discussion

Our study suggests that the relatively hypoxemic condition of cyanotic congenital heart disease is sufficient to cause a significant increase in utilization of reductive pathways for halothane metabolism. A similar increase in reductive metabolism of halothane leading to the liberation of free serum F has been previously demonstrated in rats with induced hepatic enzymes on exposure to a hypoxic halothane mixture (2,3). The serum F levels found in our C patients (mean $7.75 \pm$

Figure 3. Means with SEM for (A) serum glutamic pyruvate transaminase and serum glutamic oxaloacetate transaminase and (B) blood urea nitrogen in acyanotic and cyanotic groups of patients before and after open heart surgery. Significant within-group (*) differences are indicated.

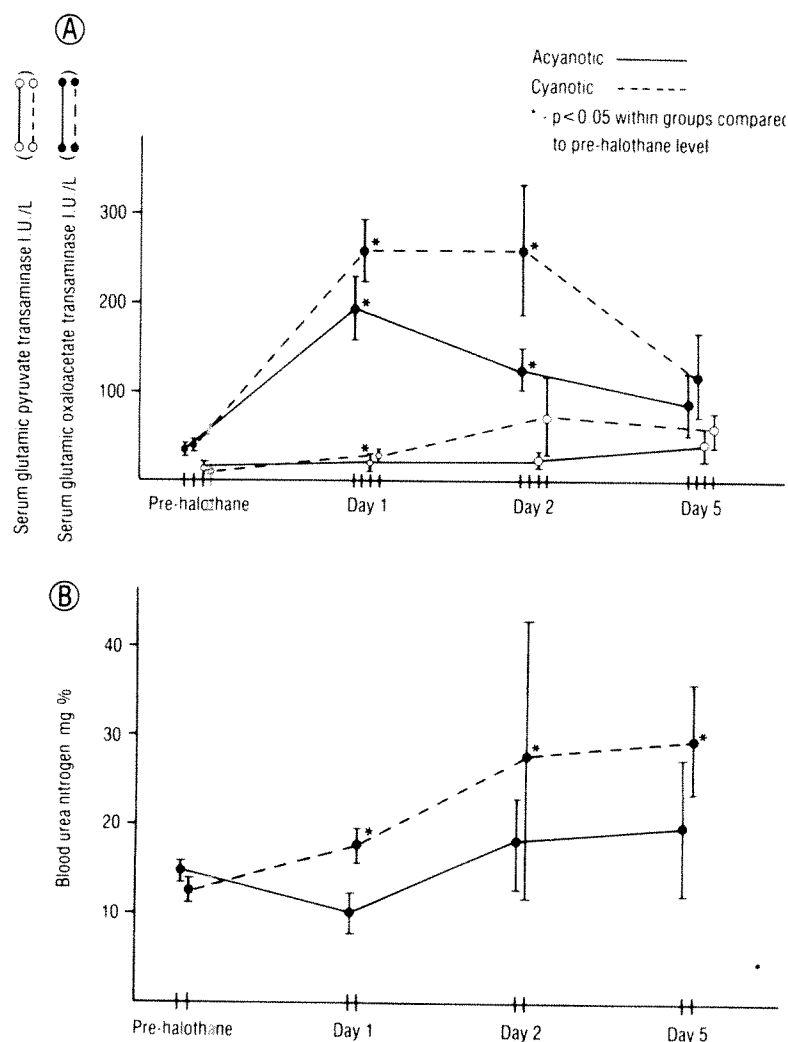


Table 2. Serum Alkaline Phosphatase and Creatinine Levels in Acyanotic and Cyanotic Groups

		Preinduction	Day 1	Day 2	Day 5
Alkaline Phosphatase (IU/L)	Acyanotic	239 ± 26	112 ± 10	115 ± 10	130 ± 9
	Cyanotic	276 ± 50	414 ± 299	115 ± 12	127 ± 19
Creatinine mg%	Acyanotic	0.61 ± 0.09	0.64 ± 0.09	0.72 ± 0.13	0.70 ± 0.23
	Cyanotic	0.57 ± 0.08	0.78 ± 0.08	0.93 ± 0.08	0.69 ± 0.08

1.71 μM , with a range of 1.34–17.55 μM) approach the levels observed in the rats surviving the combination of hypoxia and halothane exposure ($12.7 \pm 5.5 \mu\text{M}$ and $19 \pm 2 \mu\text{M}$) (2,3).

Additional data obtained on a C patient undergoing a closed heart procedure revealed a peak F level of 25.9 μM , which suggests that some factor, such as pump prime dilution, may have blunted the increase in serum F for our patients undergoing open heart surgery. Of interest, elevation in serum F was also observed in the AC patients, but not to the level at-

tained in C patients. Although utilization of reductive pathways for halothane metabolism can occur at low levels in normoxic humans (8), reductive metabolism sufficient to cause elevations in serum F during halothane exposure with adequate oxygenation has only been observed in obese patients (9).

Estimation of total anesthesia uptake on the basis of either the inspired or expired anesthetic concentration can be misleading for patients with intracardiac shunts. More exact quantitation would necessitate continuous monitoring of serum anesthetic levels.

The increase in serum halothane in patients with right-to-left shunts (cyanotics) is slower than in patients with left-to-right shunts (acyanotics) at equivalent anesthetic concentration (10,11). This delay in uptake explains the slower anesthetic induction times for patients with cyanotic heart disease (12). In our study, in spite of equivalent MAC minutes of halothane exposure for both groups, the AC patients most likely received a greater total halothane load due to the constant variation of inspired anesthetic concentration in conjunction with the lag in anesthetic intake for the cyanotic patients. Support for this is provided by the higher B and TFAA levels in the AC group. A significant contribution to serum B by pancuronium bromide can be discounted because each 0.1 mg/kg of pancuronium bromide would contribute only 1.3 μ M B assuming complete metabolism, no elimination, and a distribution volume for bromide limited to the extracellular and intravascular fluid space.

In our study, in spite of greater reductive metabolism of halothane occurring in the C group, little difference was found in derangements of postoperative hepatorenal dysfunction in this group compared with AC patients. The C patients did develop significantly higher serum bilirubin levels, but this difference had become insignificant by the fifth postoperative day. Other factors, such as a greater use of inotropes, longer ventilatory support, and generally sicker patients in the C group could have contributed to the observed difference. Therefore, no direct cause-effect relationship between increased reductive metabolism of halothane and postoperative hepatorenal derangement could be shown. However, because most of the patients in this study were children and adverse hepatic responses to halothane are rare in children, the present data may not be indicative of the hepatic response to halothane in adults under similar conditions.

In summary, after open heart surgery, patients with cyanotic heart disease developed significantly higher serum fluoride levels, indicating increased reductive

metabolism of halothane compared with a group of acyanotic patients. Both groups had similar derangements in serum hepatorenal chemistries that began normalizing by the fifth postoperative day.

The authors acknowledge Stephan T. Weldon, BS, for his expert technical assistance.

References

1. Rehder K, Forbes J, Alter H, Hessler O, Stier A. Halothane biotransformation in man: a quantitative study. *Anesthesiology* 1967;28:711-5.
2. Widger LA, Gandolfi AJ, Van Dyke RA. Hypoxia and halothane metabolism in vivo: Release of inorganic fluoride and halothane metabolite binding to cellular constituents. *Anesthesiology* 1976;44:197-201.
3. Ross WT, Daggy BP, Cardell RR. Hepatic necrosis caused by halothane and hypoxia in phenobarbital-treated rats. *Anesthesiology* 1979;51:327-33.
4. Jee RC, Sipes IG, Gandolfi AJ, Brown BR. Factors influencing halothane hepatotoxicity in the rat hypoxic model. *Toxicol Appl Pharmacol* 1980;52:267-77.
5. McLain GE, Sipes IG, Brown BR. An animal model of halothane hepatotoxicity: Roles of enzyme induction and hypoxia. *Anesthesiology* 1979;51:321-6.
6. Maiorino RM, Gandolfi AJ, Sipes IG. Gas-chromatographic method for the halothane metabolites, trifluoroacetic acid and bromide, in biological fluids. *J Anal Toxicol* 1980;4:250-4.
7. Bruning JL, Kintz BL. *Computational handbook of statistics*. Glenview, IL: Scott, Foresman and Company, 1968:199.
8. Cohen EN, Trudell JR, Edmunds HN, Watson E. Urinary metabolites of halothane in man. *Anesthesiology* 1975;43:392-401.
9. Bentley JB, Vaughan RW, Gandolfi AJ, Cork RC. Halothane biotransformation in obese and nonobese patients. *Anesthesiology* 1982;57:94-7.
10. Eger EI, Severinghaus JW. Effect of uneven pulmonary distribution of blood and gas on induction with inhalation anesthetics. *Anesthesiology* 1964;25:620-6.
11. Stoelting RK, Longnecker DE. The effect of right-to-left shunt on the rate of increase in arterial anesthetic concentration. *Anesthesiology* 1972;36:352-6.
12. Moffitt EA, McGoon DC, Ritter DG. The diagnosis and correction of congenital cardiac defects. *Anesthesiology* 1970;33:144-60.

Differential Depressant and Electrophysiologic Cardiotoxicity of Local Anesthetics:

An Experimental Study with Special Reference to Lidocaine and Bupivacaine

Sherdil Nath, MB, BS, FFARCS, Sören Häggmark, RTA, Göran Johansson, RTA, and Sebastian Reiz, MD, PhD

NATH S, HÄGGMARK S, JOHANSSON G, REIZ S.
Differential depressant and electrophysiologic cardiotoxicity of local anesthetics: an experimental study with special reference to lidocaine and bupivacaine. *Anesth Analg* 1986;65:1263-70.

In 15 pigs lidocaine and bupivacaine were injected into the left anterior descending (LAD) coronary artery to investigate the cardiotoxic effects of these drugs. Anesthesia was maintained by a continuous intravenous pentobarbital infusion and ventilation was controlled. Aortic, pulmonary arterial, right atrial, and left ventricular pressures, a standard 12 lead ECG, cardiac output, and great cardiac venous blood flow were recorded. The local anesthetics were administered at body temperature over approximately 10 sec in a random, crossover fashion at the following equipotent anesthetic doses: bupivacaine, 0.25, 0.5, 1, 2, and 4 mg; lidocaine, 1, 2, 4, 8, and 16 mg. The hemodynamic effects were short-lived, peaking about 5 sec after drug infusion. At the highest dose, both drugs decreased left ventricular dP/dT by 28% ($P < 0.001$) and aortic blood pressure by 12% (lidocaine) and 8% (bupivacaine) ($P < 0.001$ and $P < 0.01$). Heart rate, cardiac output, and coronary venous

blood flow did not change. Thus, the cardiodepressant ratio between the two drugs was comparable with their local anesthetic potency ratio (bupivacaine/lidocaine, 4:1). Seven animals died in ventricular fibrillation within 1 min after 4 mg bupivacaine dose. All animals given 16 mg lidocaine survived. Ventricular fibrillation was preceded by progressive widening of the QRS complexes recorded over the area perfused by the LAD. The ECG changes after 16 mg lidocaine were of the same magnitude as those recorded after 1 mg bupivacaine. In five of the surviving animals 32 and 64 mg lidocaine were injected intracoronarily after termination of the crossover study. After 64 mg, three animals died in sudden ventricular fibrillation, preceded by similar ECG changes as seen after 4 mg bupivacaine. Thus, the electrophysiologic toxicity ratio between bupivacaine and lidocaine was on the order of 16:1. It is concluded that this animal model is reproducible and allows discrimination between cardiodepressant and electrophysiologic toxicity of local anesthetic agents.

Key Words: ANESTHETICS, LOCAL—lidocaine, bupivacaine. HEART—contractility. TOXICITY—local anesthetics.

A few case reports of death after inadvertent intravenous bolus injections of bupivacaine and etidocaine were presented in the late 1970s (1,2). In 1979, these were followed by an editorial by Albright (3), in which he presented further anecdotal cases of fatalities with the same agents. These observations led to a large body of animal experimentation to clarify the mechanisms by which local anesthetics, in particular the

highly lipid soluble and protein bound ones of the amide type, may cause cardiovascular collapse and death.

From studies on the isolated guinea pig heart preparation, it appears that bupivacaine produces an approximately fourfold greater reduction in contractility than lidocaine on a milligram-for-milligram basis (4). Thus, the relative cardiotoxicity with regards to cardiodepression is the same as the anesthetic potency ratio between the drugs (5). In comparison, bupivacaine was 10–16 times more potent than lidocaine when the effects of the agents on the maximal rate of rise of the cardiac action potential (V_{max}) were recorded (6,7). These studies indicate that the affinity for and duration of binding to the sodium channel may explain the great difference in electrophysiologic

Presented in part at the Swedish Anesthesia Society Meeting, September 1985.

Received from the Department of Anesthesiology, University of Umeå, Umeå, Sweden. Accepted for publication June 27, 1986.

Address correspondence to Dr. Nath, Department of Anesthesiology, University Hospital, S 901 85 Umeå, Sweden.

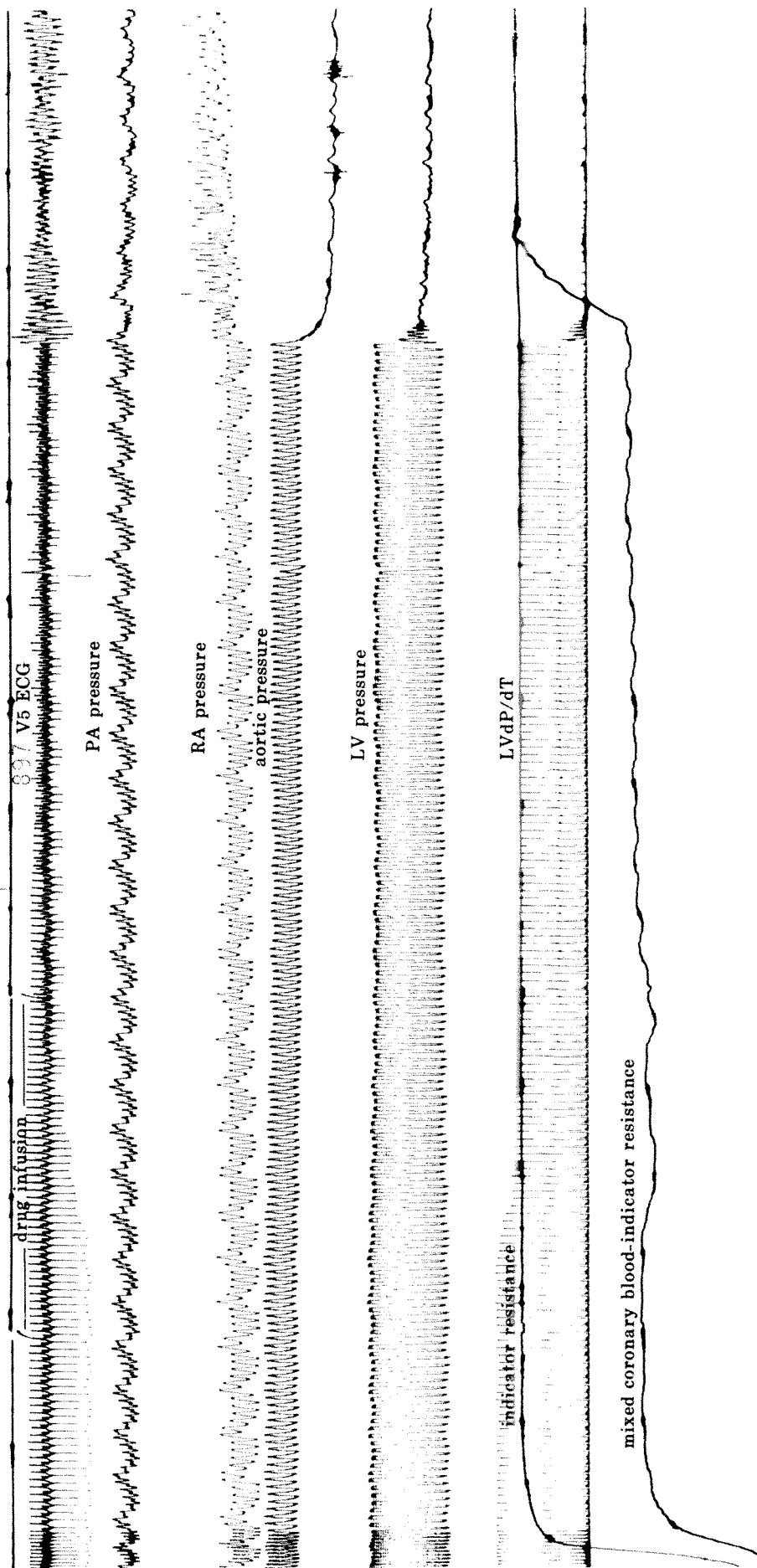


Figure 1. Effects of 4 mg of intracoronarily injected bupivacaine on the V5 ECG, on pulmonary arterial (PA), right atrial (RA), aortic, and left ventricular (LV) pressures, on left ventricular dP/dT and on coronary blood-indicator resistance. Sudden ventricular fibrillation, preceded by one premature ventricular contraction, occurred 33 sec after the end of drug administration. Despite an approximately 30% reduction in LVdP/dT, only small changes were observed in systemic blood pressure and pulmonary artery pressure.

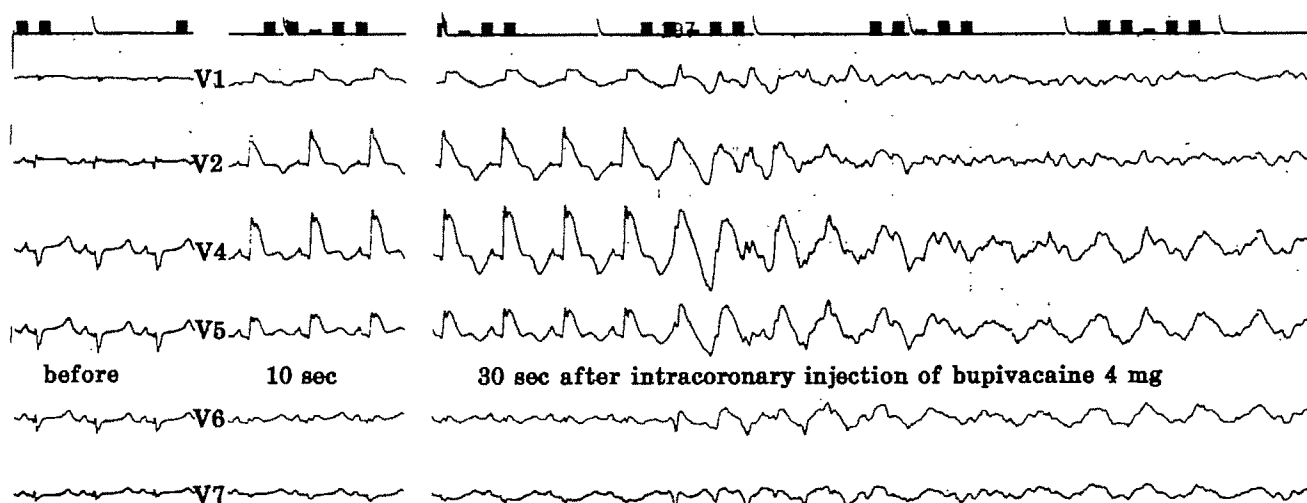


Figure 2. ECG chest lead recordings from the animal shown in Figure 1. Ventricular fibrillation was preceded by progressive widening of the QRS complexes recorded over the area of the myocardium perfused by the left anterior descending artery. Leads V6 and monitoring the area perfused by the circumflex artery showed only minor changes.

cardiac toxicity ratio between the local anesthetics. They also suggest that the arrhythmias, so frequently recorded in association with animal experimentation *in vivo* (8-10), might be due to reentrant phenomena.

Recently, bupivacaine and lidocaine injected directly into the nucleus tractus solitarius of the rat spinal cord have been shown to produce both cardiovascular changes and ECG abnormalities similar to those recorded after a massive intravenous dose of the drugs (11).

We present an *in vivo* animal model, with which the negative cardiac inotropic and electrophysiologic toxicity ratios for local anesthetic agents may be determined without the risk of central nervous system (CNS)-mediated interaction. The model is described with special reference to the cardiotoxic effects of lidocaine and bupivacaine.

Methods

Anesthetic and Measurement Procedures

After approval by the Swedish animal experimentation committee, 15 pigs weighing 45-50 kg were used for the study. Food and water were withheld from midnight preceeding the day of investigation. After being anesthetized with intravenous pentobarbital 15 mg/kg, tracheostomy was performed and the animals were attached to a Siemens-Elcoma Servoventilator 900B. Ventilation with oxygen-enriched air (FI_{O_2} 0.3) was adjusted to maintain an end-tidal PCO_2 around 4.5 kPa (34 mm Hg). Light anesthesia was maintained by a continuous central venous infusion of pentobarbital. The plasma concentrations of the anesthetics

were determined at regular intervals throughout study period by high performance liquid chromatography. After cutdown, the following catheters were inserted with the aid of fluoroscopy: a 7F flow direct pulmonary artery thermodilution catheter, a 7F Webster thermodilution catheter into the great cardiac vein draining the area perfused by the left anterior descending coronary artery (LAD), and a precalibrated 7F Millar tip transducer left ventricular catheter. After systemic heparinization with 5000 IU, a 4F Teflon catheter was introduced over a guide wire and placed into the LAD, just distal to the bifurcation with circumflex artery. The coronary arterial and venous catheters were maintained in a constant position confirmed by fluoroscopy before and after the drug administrations.

A 12-lead ECG, aortic, pulmonary arterial, right atrial pressures, and left ventricular dP/dT were recorded continuously on Mingograph recorders 62 and 82 throughout the study. Heart rate was derived from the ECG recording. Water standards were placed at 0 (midchest) and 50 mm Hg. Cardiac output was determined in triplicate using 5 ml of ice-cold normal saline for each measurement. The indicator was pneumatically injected over 1.2 sec by an ATI-1 pump synchronized to end-expiration. Cardiac output was determined before and 60 sec after each dose of local anesthetic agent. Great cardiac venous blood flow was determined by the continuous, retrograde thermocolor dilution technique (12). Normal saline at room temperature was used as the indicator and injected at approximately 40 ml/min for each measurement. The flow measurement was started approximately 10

before drug injection and continued until 60 sec after termination of drug administration. Corrections for indicator loss within the catheter and for recirculation errors were made from model experiments on each catheter used (13,14).

Intracoronary Drug Administration

Placebo injection of 2 ml normal saline at body temperature was done before and after each series of local anesthetic. Each local anesthetic dose was made up to a volume of 2 ml with normal saline and preincubated at body temperature before being injected. The intracoronary injection rate of the local anesthetics was corrected for coronary blood flow at the time of injection to produce a true stepwise increase in tissue exposure to the dose, over time. Bupivacaine and lidocaine were administered in a random, crossover fashion with stepwise increasing doses. The following doses of bupivacaine were administered: 0.25, 0.5, 1.0, 2.0, and 4.0 mg. Lidocaine was administered in anesthetically equipotent doses of 1.0, 2.0, 4.0, 8.0, and 16.0 mg. In order to establish the lethal dose of lidocaine, five of the surviving animals were also given 32 and 64 mg intracoronarily following the 16 mg lidocaine or 4 mg bupivacaine dose. An interval of 5 min, or longer if the ECG and hemodynamics had not returned to baseline, was allowed between consecutive doses of the local anesthetics. A washout period of 1 hr was allowed between the two local anesthetic agents.

Statistics

The χ^2 -test, the Wilcoxon test, and the Mann-Whitney test were used for statistical analyses of the results, which are presented as means \pm SEM. A *P* value less than 0.05 was regarded as statistically significant.

Results

The plasma concentration of pentobarbital remained constant throughout the investigation. Fifteen animals were given bupivacaine; 11 received lidocaine. The difference in group size was due to death from ventricular fibrillation in four animals randomized to receive bupivacaine as their first drug. Another three animals died after bupivacaine was administered as the second drug. All seven animals died after the 4 mg dose (Figs. 1, 2; Table 1). Three of the five animals that went on to receive 64 mg of lidocaine died in a manner similar to that observed in animals given bupivacaine, including sudden onset of ventricular

Table 1. Outcome and Cause of Death

Animal number	First drug	Second drug	Outcome/cause of death
1	B	—	VF 52 sec after 4 mg of B
2	L	B	survived
3	B	L	survived
4	B	—	VF 20 sec after 4 mg of B
5	L	B	VF 30 sec after 4 mg of B
6	L	B	survived
7	B	L	survived
8	B	—	VF 9 sec after 4 mg of B
9	L	B	survived
10	B	L	survived
11	L	B	VF 33 sec after 4 mg of B
12	B	—	VF 8 sec after 4 mg of B
13	L	B	survived
14	L	B	VF 1 sec after 4 mg of B
15	L	B	survived

L, lidocaine; B, bupivacaine; VF, ventricular fibrillation.

brillation (Figs. 3, 4). Resuscitation was unsuccessful in all animals developing ventricular fibrillation.

None of the placebo injections caused any significant systemic, central, or coronary hemodynamic changes. The hemodynamic effects of both lidocaine and bupivacaine were short-lived, peaking at 5 sec and returning to baseline values within 60 sec. Five seconds after the end of the intracoronary injection of the highest dose (4 mg bupivacaine and 16 mg lidocaine), the agents decreased mean arterial pressure by 8% ($P < 0.01$) and 12% ($P < 0.001$), respectively, and increased left ventricular end-diastolic pressure (LVEDP) by 24 and 29%, respectively ($P < 0.001$; difference between drugs not significant); whereas, heart rate, cardiac output, and stroke volume remained unchanged. Left ventricular dP/dT decreased in a dose-related fashion. We recorded comparable peak reductions after 4 mg bupivacaine (-28% , $P < 0.001$) and 16 mg lidocaine (-28% , $P < 0.001$). The effects of the two drugs on coronary hemodynamics were negligible after all doses. The circulatory responses to 4 mg bupivacaine, thus, were not statistically different from those of 16 mg lidocaine (Table 2).

None of the placebo injections produced any electrocardiographic changes. The 12-lead ECG showed marked, dose-dependent alterations in the V1-V4 leads following injection of bupivacaine into the left anterior descending coronary artery. These were characterized mainly by widening of the QRS complex and change in T-wave polarity and electrical axis (Figs. 2, 4). The QRS interval increased by 132% ($P < 0.001$) and the QT interval by 21% ($P < 0.001$) after 4 mg bupivacaine, whereas, the PQ interval remained unaltered (Table 3). Lidocaine produced moderate ECG

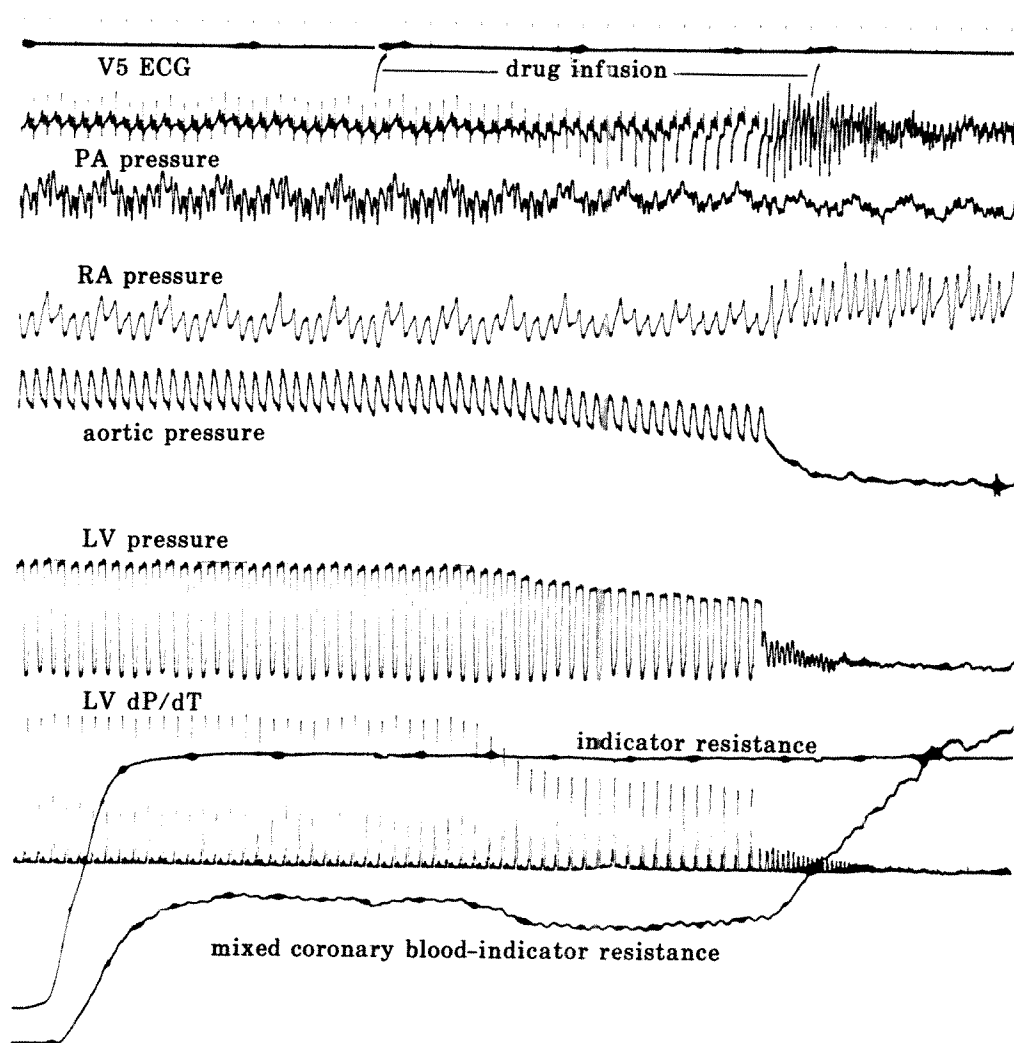


Figure 3. Sudden onset of ventricular fibrillation during intracoronary injection of 64 mg lidocaine. Hemodynamic changes were more pronounced than those observed after 4 mg bupivacaine (Fig. 1).

changes, mainly T-wave abnormalities at the 8- and 16-mg doses comparable with those seen with the 0.5- and 1-mg bupivacaine doses (Fig. 5), but did not cause any prolongation of the PQ, QT, or QRS intervals (Table 3). The subgroup of surviving animals given 32 and 64 mg lidocaine demonstrated dose-related prolongation of the QRS and QT intervals comparable with those recorded after 2 and 4 mg bupivacaine (Table 3). Unlike the hemodynamics, which returned to normal within 60 sec in the surviving animals, the ECG changes persisted for up to 6 min after the highest doses of lidocaine and bupivacaine.

Discussion

The experimental model used was specifically aimed at comparing the action of bupivacaine and lidocaine

on cardiac force of contraction and electrophysiology without interference from the CNS. This requires intracoronary administration of the drugs. Because the agents were injected into the LAD, a major portion of the left ventricle was exposed. The SA- and AV-node conduction were not affected. Furthermore, zones of depolarization might be established in the left ventricle, resulting in reentry phenomena. Accordingly, neither the magnitude of hemodynamic changes recorded, nor the severity of dysrhythmias observed represent the clinical situation, where the entire heart is exposed to the drug.

Both lidocaine and bupivacaine produced dose-dependent cardiodepression peaking 5 sec after the end of injection (Table 2). Following the highest doses we recorded an approximately 30% reduction in left ventricular end-diastolic pressure (LVdP/dT) and an

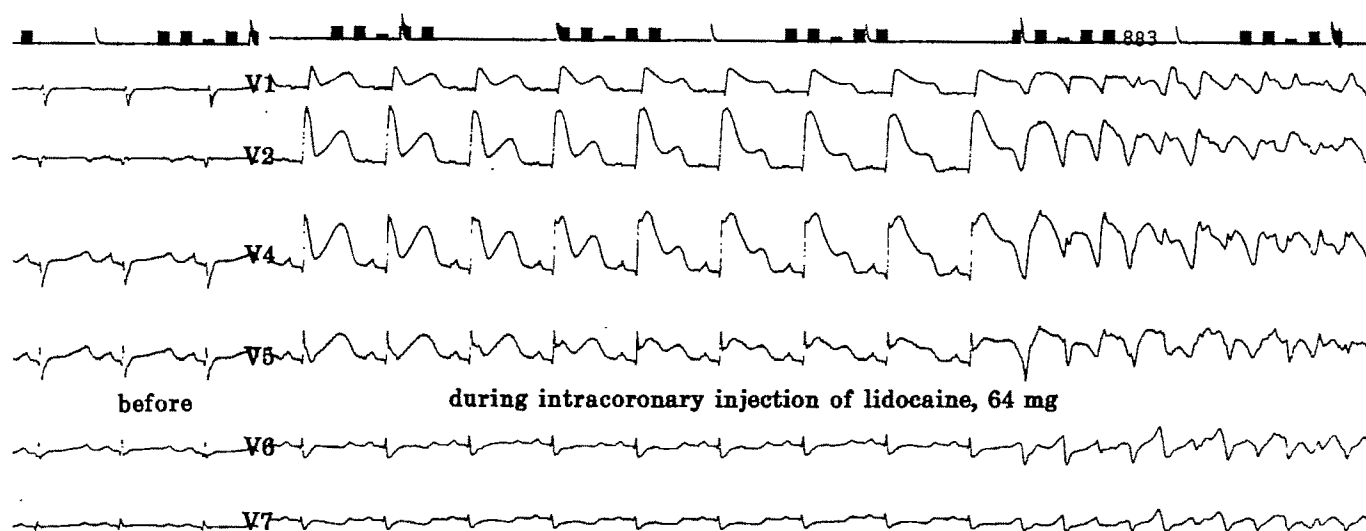


Figure 4. ECG chest lead recordings from the animal shown in Figure 3. Electrophysiologic changes were similar to those observed after 4 mg bupivacaine (Fig. 2).

increase in LVEDP of about 25%. The cardiodepressant ratio between lidocaine and bupivacaine was 1:4, which is comparable with their local anesthetic potency ratio (5). These results concur with those obtained by Feldman et al. (4) in the isolated guinea pig heart preparation and by Liu et al. (15) in the deeply pentobarbital-anesthetized, mechanically ventilated dog, after intravenous bolus doses of bupivacaine and lidocaine. Liu et al. found death to be the result of progressive cardiodepression. Their results conflict with ours and the findings of other investigators in the intact animal, most of which demonstrate ventricular dysrhythmias and conduction disturbances to be the primary cause of death (8-10). In our study, seven of 15 animals given 4 mg bupivacaine into the LAD developed ventricular fibrillation within the first minute after its administration (Table 1; Figs. 1 and 2). In comparison, 16 mg lidocaine did not produce dysrhythmias in any animal. When the lidocaine dose was increased to 32 and 64 mg in five surviving animals, the drug produced ventricular fibrillation and death at the highest dose in three animals (Figs. 3 and 4). Ventricular fibrillation was preceded by a dose-dependent widening of the QRS complex in the leads monitoring the area of the myocardium perfused by the LAD. In comparison, the lateral wall ECG leads (V6, V7), monitoring the area perfused by the circumflex artery, did not show any QRS prolongation (Figs. 2 and 4). For the same reason, atrioventricular conduction time was not affected by either drug (Table 3). Warning dysrhythmias preceded the sudden onset of ventricular fibrillation in one animal only. Electro-

physiologic recovery was significantly slower than hemodynamic following both drugs. However, it was not longer for bupivacaine than for lidocaine. Thus, bupivacaine was approximately 16 times more potent than lidocaine in prolonging ventricular conduction time. In addition, 4 mg of intracoronarily administered bupivacaine was significantly more lethal than 16 mg lidocaine ($P < 0.01$).

Electrophysiologic studies have demonstrated that local anesthetics depress the maximal rise of the cardiac action potential (V_{max}) in a dose-dependent manner, depending on membrane potential and rate of stimulation (16). V_{max} is largely dependent on the sodium ion influx via the sodium channels. It has been shown that local anesthetics bind to specific sites within the sodium channels, which can be reached by hydrophobic and/or hydrophilic pathways (17,18). Thus, highly lipid soluble molecules could reach their site directly throughout the membrane phase, whereas, the binding site is accessible for the more polar compounds only when the channel is open. Clarkson and Hondeghem (6) demonstrated a similar onset time for the block of sodium channels by high concentrations of lidocaine and bupivacaine. V_{max} was severely depressed by bupivacaine (1 $\mu\text{g}/\text{ml}$) at pacing rates from 50 to 100/min, whereas, lidocaine (10 $\mu\text{g}/\text{ml}$), in this pacing range, did not cause any depression of V_{max} . At pacing rates above 150/min, lidocaine depressed V_{max} in a fashion similar to bupivacaine. Time to return to normal V_{max} was five to six times longer after 1 $\mu\text{g}/\text{ml}$ bupivacaine than after 5 $\mu\text{g}/\text{ml}$ lidocaine. Recovery from block was always slow with bupivacaine

Table 2. Peak Hemodynamic Effects of Intracoronary Administration of Lidocaine and Bupivacaine

Lidocaine dose (mg)	Baseline	Placebo	1	2	4	8	16
MAP (mm Hg)	116 ± 5	115 ± 5	116 ± 5	113 ± 5	112 ± 5	108 ± 5	102 ± 4 ^a
HR (beats/min)	157 ± 9	157 ± 9	156 ± 9	155 ± 9	156 ± 9	155 ± 10	157 ± 9
LVEDP (mm Hg)	9.0 ± 1.0	9.8 ± 0.8	9.9 ± 0.9	10.0 ± 0.9	10.4 ± 0.9	10.6 ± 0.9	11.6 ± 0.8 ^b
LVdP/dT (mm Hg/sec)	2977 ± 184	2980 ± 176	2879 ± 186	2738 ± 197	2604 ± 185	2340 ± 160	2139 ± 150 ^b
CO (L/min)	5.5 ± 0.3	5.7 ± 0.3	5.8 ± 0.4	6.1 ± 0.3	6.3 ± 0.4	6.2 ± 0.4	6.2 ± 0.4
GCVF (ml/min)	105 ± 16	105 ± 15	116 ± 16	113 ± 15	115 ± 16	119 ± 13	113 ± 14
Bupivacaine dose (mg)			0.25	0.5	1	2	4
MAP (mm Hg)	109 ± 4	110 ± 4	110 ± 4	110 ± 4	109 ± 4	106 ± 4	100 ± 4 ^a
HR (beats/min)	156 ± 8	156 ± 8	157 ± 8	156 ± 8	156 ± 8	155 ± 8	152 ± 8
LVEDP (mm Hg)	9.7 ± 0.6	9.7 ± 0.6	10.8 ± 0.6	10.6 ± 0.6	11.1 ± 0.6	11.5 ± 0.6	12.0 ± 0.7 ^b
LVdP/dT (mm Hg/sec)	2996 ± 132	3005 ± 132	2897 ± 127	2816 ± 137	2684 ± 144	2542 ± 143	2148 ± 119 ^b
CO (L/min)	5.9 ± 0.3	6.0 ± 0.3	6.2 ± 0.3	6.2 ± 0.3	6.3 ± 0.3	6.4 ± 0.3	6.0 ± 0.5
GCVF (ml/min)	100 ± 12	99 ± 11	98 ± 12	99 ± 12	99 ± 11	98 ± 11	88 ± 9

Mean ± SEM.

For lidocaine, *n* = 11. For bupivacaine, *n* = 15.

Abbreviations: MAP, mean aortic pressure; HR, heart rate; LVEDP, left ventricular end diastolic pressure; LVdP/dT, left ventricular pressure rise over time; CO, cardiac output; GCVF, great cardiac venous blood flow.

^a*P* < 0.01.^b*P* < 0.001 compared with baseline.

Table 3. Effects of Intracoronarily Administered Lidocaine and Bupivacaine on the PQ, QRS, and QT Intervals

Lidocaine dose (mg)	Baseline	Placebo	1	2	4	8	16	32	64
PQ (csec)	10.4 ± 0.2	10.4 ± 0.2	10.4 ± 0.2	10.4 ± 0.2	10.5 ± 0.3	10.5 ± 0.3	10.6 ± 0.3	11.0 ± 0.6	11.4 ± 0.7
QRS (csec)	6.5 ± 0.5	6.5 ± 0.5	6.5 ± 0.5	6.5 ± 0.6	6.5 ± 0.6	6.5 ± 0.6	6.5 ± 0.6	9.5 ± 0.8	14.0 ± 0.9
QT (csec)	28.3 ± 1.8	28.3 ± 1.8	28.2 ± 1.8	28.1 ± 1.8	28.3 ± 1.8	28.5 ± 1.8	28.5 ± 1.9	30.6 ± 2.0	34.8 ± 1.9
Bupivacaine dose (mg)			0.25	0.5	1	2	4		
PQ (csec)	10.6 ± 0.4	10.6 ± 0.4	10.6 ± 0.4	10.7 ± 0.4	10.7 ± 0.4	11.2 ± 0.6	11.5 ± 0.6	—	—
QRS (csec)	6.0 ± 0.4	6.0 ± 0.4	6.1 ± 0.4	6.3 ± 0.4	6.6 ± 0.4	9.0 ± 0.5 ^b	13.9 ± 0.6 ^b	—	—
QT (csec)	28.5 ± 1.5	28.4 ± 1.5	28.5 ± 1.5	28.7 ± 1.4	28.9 ± 1.5	30.3 ± 1.5	34.5 ± 1.9 ^a	—	—

Mean ± SEM.

For lidocaine, *n* = 11. For bupivacaine, *n* = 15, except for the 32- and 64-mg lidocaine doses, where *n* = 5.^a*P* < 0.05.^b*P* < 0.001 compared with anesthetically equipotent lidocaine dose.

and the block could accumulate even at low heart rates. In their in vitro model, Clarkson and Hondeghem (6) demonstrated an electrophysiologic toxicity ratio between bupivacaine and lidocaine of approximately 15:1 in the physiologic heart rate range. In comparison, Komai and Rusy (19) found the ratio between bupivacaine and lidocaine for slowing the rat ventricular rate to 50% of control to be 14:1. The corresponding ratio for doubling the PR interval was 17:1. Moller and Covino (7) exposed the right bundle of the rabbit heart to normal and toxic doses of lidocaine and bupivacaine. They found bupivacaine to be more than tenfold more potent than lidocaine in depressing a number of electrophysiologic variables of the transmembrane action potential, recorded from both Purkinje fibers and ventricular muscle cells. As did Clarkson and Hondeghem (6), Moller and Covino

found the duration of block to be considerably longer after bupivacaine than after lidocaine.

In our animal model we have found the cardio-depressant toxicity ratio between bupivacaine and lidocaine to be 4:1, which is the same as their anesthetic potency ratio. Cardiodepression, however, was not the cause of death in this animal model. As in most other animal models, death due to local anesthetics was the result of electrophysiologic disturbances, characterized by progressive prolongation of ventricular conduction time preceding a sudden onset of ventricular fibrillation. The electrophysiologic toxicity ratio between bupivacaine and lidocaine in our model was 16:1, which is comparable with that obtained in a number of preparations in vitro. Slowed ventricular conduction predisposes for reentrant phenomena (20), explaining the sudden onset of ventricular dysrhythmia.

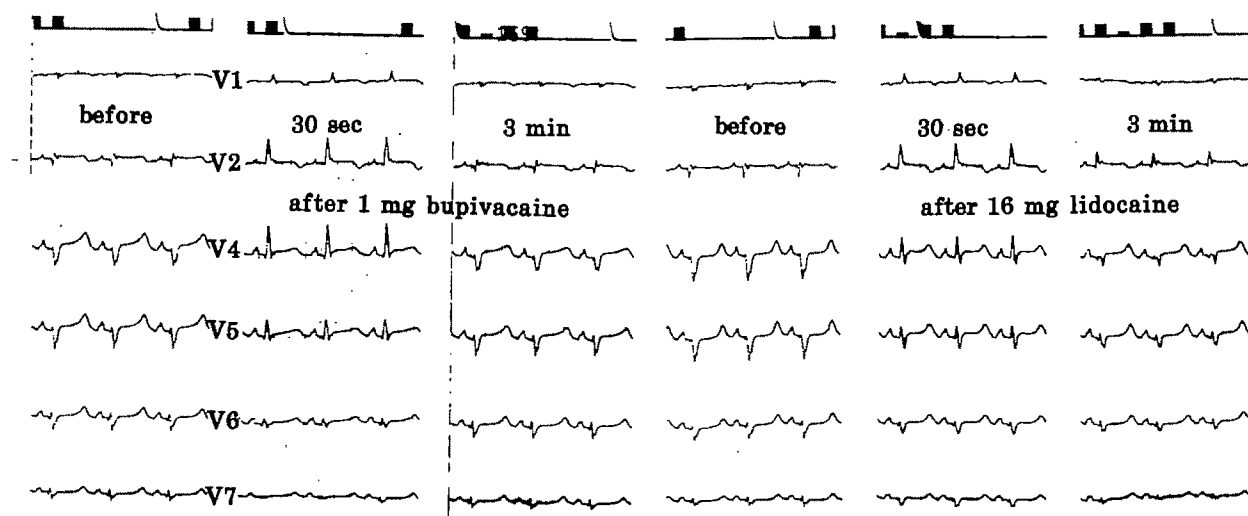


Figure 5. ECG chest leads before and following intracoronary injections of 1 mg bupivacaine and 16 mg lidocaine in the same animal. Similar electrophysiologic changes were observed after these doses.

mas reported in the present and other studies of the cardiovascular effects of toxic doses of bupivacaine.

References

1. Edde RR, Deutsch S. Cardiac arrest after interscalene brachial plexus block. *Anesth Analg* 1977;56:446-447.
2. Prentiss JE. Cardiac arrest following caudal anesthesia. *Anesthesiology* 1979;50:51-53.
3. Albright GA. Cardiac arrest following regional anesthesia with etidocaine or bupivacaine. *Anesthesiology* 1979;51:285-287.
4. Feldman HS, Covino BM, Sage DJ. Direct chronotropic and inotropic effects of local anesthetic agents in isolated guinea pig atria. *Regional Anesthesia* 1982;7:149-156.
5. Gissen AJ, Covino BG, Gregus J. Differential sensitivity of mammalian nerve fibers to local anesthetic agents. *Anesthesiology* 1981;53:467-474.
6. Clarkson CW, Hondeghem LM. Mechanism for bupivacaine depression of cardiac conduction: Fast block of sodium channels during the action potential with slow recovery from block during diastole. *Anesthesiology* 1985;62:396-405.
7. Moller RA, Covino BG. Toxic cardiac electrophysiologic effects of bupivacaine and lidocaine at high concentration. *Anesthesiology* 1985;63:A223.
8. de Jong RH, Davis NL. Treating bupivacaine arrhythmias: Preliminary report. *Regional Anesthesia* 1981;6:99-103.
9. Kotelko DM, Shnider SM, Dailey PA, Brizgys RV, Levinson G, Shapiro WA, Koike M, Rosen MA. Bupivacaine-induced cardiac arrhythmias in sheep. *Anesthesiology* 1984;60:10-18.
10. Morishima HO, Pedersen H, Finster M, Hiraoka H, Tsuji A, Feldman HS, Arthur GR, Covino BG. Bupivacaine toxicity in pregnant and nonpregnant ewes. *Anesthesiology* 1985;63:134-139.
11. Thomas RD, Behbehani MM, Coyle DE, Denson DD. Cardiovascular system toxicity with local anesthetics: An alternative hypothesis. *Anesthesiology* 1985;63:A228.
12. Ganz W, Tamura K, Marcus HS, Donoso R, Yoshida S, Swan HJC. Measurement of coronary sinus blood flow by continuous thermodilution in man. *Circulation* 1971;44:181-195.
13. Reiz S, Häggmark S. Coronary sinus catheterisation and measurement of coronary sinus blood flow by the continuous thermodilution method. In: Prys-Roberts C, Vickers MD, eds. *Cardiovascular measurement in anaesthesiology*. Proceedings of the European Academy of Anaesthesiology. Berlin: Springer Verlag, 1981;174-182.
14. Bålfors E, Häggmark S, Ariola Jr S, Biber B, Pontén J, Reiz S. In vitro analysis of thermal transport in coronary sinus thermodilution catheters. *Clin Physiol* 1983;3:469-476.
15. Liu P, Feldman HS, Covino BM, Giasi R, Covino BG. Acute cardiovascular toxicity of intravenous amide local anesthetics in anesthetized ventilated dogs. *Anesth Analg* 1982;61:317-322.
16. Boyden PA, Wit AL. Pharmacology of the antiarrhythmic drug. In: Rosen MR, Hoffman BF, eds. *Cardiac therapy*. Amsterdam: Nijhoff, 1983;171-234.
17. Hille B. Local anesthetics: Hydrophilic and hydrophobic pathways for drug-receptor reaction. *J Gen Physiol* 1977;67:497-515.
18. Hondeghem LM, Katzung BG. Time- and voltage-dependent interactions of antiarrhythmic drugs with cardiac sodium channels. *Biochem Biophys Acta* 1977;472:373-398.
19. Komai H, Rusy BF. Effects of bupivacaine and lidocaine on AV conduction in the isolated rat heart: modification by hyperkalemia. *Anesthesiology* 1981;55:281-285.
20. Singer DH, Baumgarten CM, Ten Eick RE. Cellular electrophysiology of ventricular and other dysrhythmias: studies on diseased and ischemic heart. *Prog Cardiovasc Dis* 1981;24:97-156.

Protamine: Does It Alter Right Ventricular Function?

Roberta L. Hines, MD, and Paul G. Barash, MD

HINES RL, BARASH PG. Protamine: does it alter right ventricular function? *Anesth Analg* 1986;65:1271-4.

Protamine administration has been associated with cardiac decompensation secondary to acute pulmonary vasoconstriction and subsequent right ventricular failure. To determine whether protamine infusion produced alterations in right ventricular performance, we evaluated both right and left ventricular function in patients receiving protamine infusion. The dose of protamine administered was calculated as adequate to reverse heparin as measured by the activated clotting time (ACT). Indices of right and left ventricular function obtained included right atrial pressure, right ventricular pressure, right ventricular ejection fraction, pulmonary artery pressure, pulmonary capillary wedge pressure, cardiac output, blood pressure, and heart rate. These measurements were obtained prior to protamine adminis-

tration, at 1/2 total protamine dose, at completion of protamine infusion, and prior to sternal closure. No significant changes in right ventricular ejection fraction, right ventricular end-diastolic pressure, mean pulmonary artery pressure, or pulmonary vascular resistance were seen at any point during the study. Left ventricular function remained unchanged. Even in patients who are possibly at an increased risk (pulmonary artery hypertension, PAP > 25 mm Hg), no deterioration in right or left ventricular function could be demonstrated following protamine administration. These data suggest that protamine does not consistently exert a significant detrimental effect on right ventricular performance.

Key Words: BLOOD, COAGULATION—protamine. HEART—ventricular function. LUNGS—vasculature.

Protamine administration has been associated with right ventricular (RV) failure and subsequent cardiac decompensation. Although many studies imply a predominant vasodilator action, recent reports suggest that pulmonary vasoconstriction following protamine infusion is the principle event leading to RV failure (1-3). Lowenstein et al. described five patients who developed severe hemodynamic instability when intravenous protamine was infused following cardiopulmonary bypass (3). Cardiovascular changes were manifested as elevations of pulmonary artery pressure and decreases in left atrial pressure. These alterations in cardiac performance were attributed to RV dysfunction secondary to an increase in pulmonary vascular resistance. We also have observed similar reactions. Because previous investigations have not specifically focused on the response of the right ventricle to protamine infusion, we decided to inves-

tigate both right and left ventricular function in patients receiving protamine infusion. Our aim was to determine if a consistent change in RV function could be observed following protamine administration.

Methods

Using a protocol approved by the Human Investigation Committee, 25 patients ($n = 25$), with a mean age of 64 years scheduled to undergo coronary artery bypass grafting (CABG) ($n = 13$), or valvular ($n = 12$) surgery were evaluated. Ninety minutes prior to arrival in the operating room, patients were premedicated with intramuscular morphine 0.1 mg/kg and scopolamine 0.4 mg. Intravenous and arterial catheters were placed percutaneously under local anesthesia. Induction was performed with fentanyl 50 $\mu\text{g/kg}$, and pancuronium 0.1 mg/kg was utilized for muscle relaxation. For maintenance of anesthesia, enflurane was titrated as clinically indicated. Ventilation was maintained using an $\text{FI}_{\text{O}_2} = 1.0$. After successful weaning from cardiopulmonary bypass and with stable hemodynamics, the study was initiated. Stable hemodynamics are defined as an adequate cardiac index ($>2.5 \text{ L}\cdot\text{min}^{-1}\cdot\text{m}^{-2}$), with a pulmonary

Paper presented in part at the Annual Meeting of the International Anesthesia Research Society, Houston, Texas, March 1985.

Received from the Department of Anesthesiology, Yale University School of Medicine, New Haven, Connecticut. Accepted for publication June 27, 1986.

Address correspondence to Dr. Hines, MD, Assistant Professor of Anesthesiology, Department of Anesthesiology, Yale University School of Medicine, 333 Cedar Street, New Haven, CT 06510.

capillary wedge pressure (PCWP) of 10–15 mm Hg in the CABG patients and a PCWP of 15–20 mm Hg in the valve patients; without the need for additional inotropic support. No additional vasoactive drug therapy was initiated during the study period. Hemodynamic measurements were recorded at end exhalation for the following events: preprotamine infusion, 50% total protamine infusion, completion of protamine infusion, and presternal closure. Measured variables included: right atrial pressure (RAP), right ventricular pressure (RVP), right ventricular ejection fraction (RVEF), pulmonary artery pressure (PAP), PCWP, cardiac output, blood pressure, and heart rate. Right ventricular ejection fraction was computed using diastolic washout plateaus of a thermal dilution cardiac output curve obtained with a rapid response thermistor (50 msec) Swan-Ganz catheter. The response time of these catheters is rapid enough to facilitate recording of beat-to-beat temperature variation and, thus, allows for calculation of RVEF by indicator dilution methods. Catheter position, with placement of the thermistor just proximal to the tricuspid valve, was verified before each ejection fraction determination. Kay et al. have validated this technique with radionuclear studies both in an animal model and in patients after open heart surgery (4). Subsequently, Jardin et al. also validated this technique using echocardiography (5). The normal value for RVEF measured via this technique is approximately 40%.

The amount of protamine was calculated to reverse residual heparin as measured by the activated clotting time using a dose-response curve according to the method of Bull et al. (6). There were no statistically significant differences in mean protamine dosage or duration of administration within either of our patient groups. The mean dose of protamine given was calculated at $493 \text{ mg} \pm 12.2 \text{ SD}$ in the patients undergoing CABG and $500 \text{ mg} \pm 11.9 \text{ SD}$ in the patients receiving valve replacement. The mean duration of protamine administration was $19.5 \pm 1.3 \text{ min}$ and $21 \pm 1.8 \text{ min}$, respectively. This rate of infusion is consistent with standards for protamine administration at our institution. Data are expressed as the mean \pm SD. Statistical evaluation was performed by one-way analysis of variance, $P < 0.05$ was considered significant.

Results

One hundred ($n = 100$) hemodynamic profiles were collected from 25 patients. No alteration in RV function was observed during or following protamine administration. Specifically, in the patients undergoing CABG ($n = 13$), RV end-diastolic pressure did

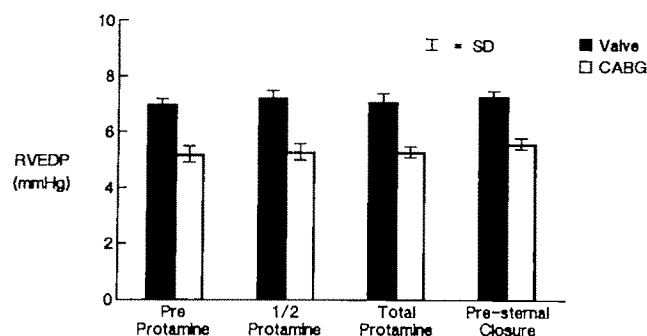


Figure 1. Right ventricular end-diastolic pressure (RVEDP) measurements obtained before, during, and after protamine administration.

not significantly change from baseline ($5 \text{ mm Hg} \pm 8$). Similarly, in the valve patients ($n = 12$), the preprotamine RV end-diastolic pressure ($7 \text{ mm Hg} \pm 7$) remained constant throughout the study period (Fig. 1). In both patient groups heart rate and mean PAP were unchanged following protamine administration (Fig. 2).

The mean RVEF measured in the preprotamine period was found to be $37\% \pm 4.6$ in the CABG patients and $33\% \pm 5.1$ in the valve population (Fig. 3). These values were unchanged following protamine infusion. Likewise, no statistically significant alterations in left ventricular function were detected in the cardiovascular response to protamine within either patient population (Fig. 2).

To determine if pulmonary artery hypertension is a risk factor we examined right and left ventricular function in a subset of patients with pulmonary artery hypertension. We defined pulmonary artery hypertension as a mean PAP prior to protamine infusion of $\geq 25 \text{ mm Hg}$ (not due to fluid overload). Using this criteria, six of 12 valve patients had evidence of pulmonary artery hypertension. In these patients, RV performance as measured by RVEDP and RVEF failed to reveal any deterioration in RV function during or following protamine infusion. The preprotamine RVEF (30%) did not differ significantly from the presternal closure valve (RVEF = 31%) (Fig. 4).

Discussion

Our observations, like those of Lowenstein et al. (3), have shown episodes of right ventricular failure following protamine infusion; however, our data suggests that protamine does not exert a significant detrimental effect on RV function. In agreement with Horrow (7), we postulated that these reactions occur infrequently. The isolated episodes of RV failure previously reported after protamine infusion may be hy-

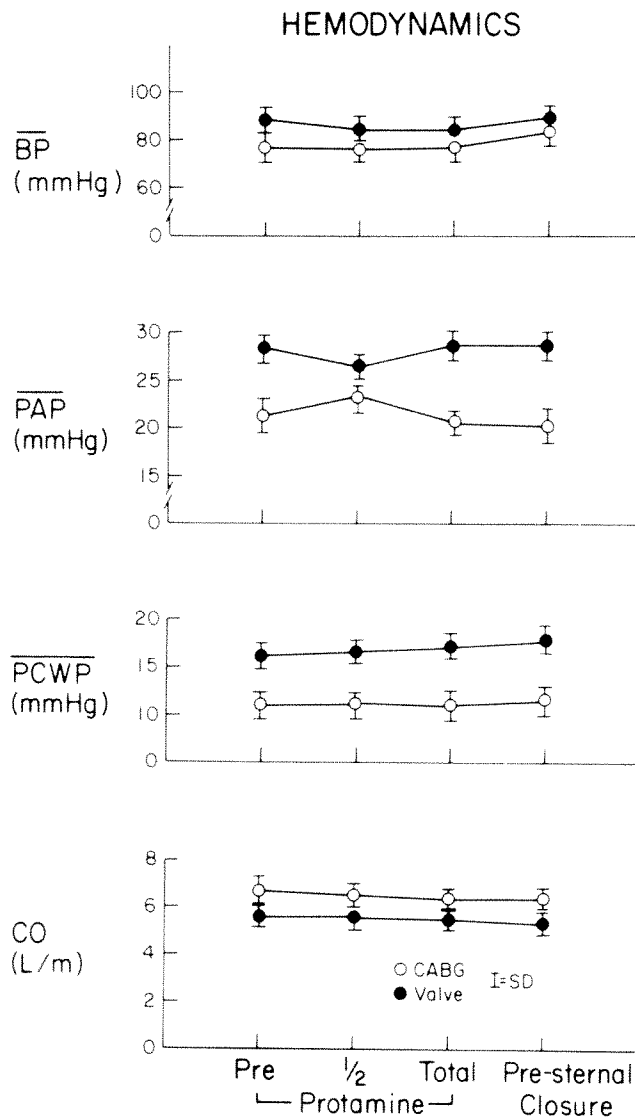


Figure 2. Indices of left ventricular function as measured in relation to protamine infusion.

pothesized to occur on the basis myocardial depression, systemic vasodilation (8), histamine release (9), hypocalcemia (10), anaphylactoid response not involving antibodies thought to be mediated by complement activation (11,12), and increases in pulmonary vascular resistance (3).

Numerous investigators have implicated direct myocardial depression as a causative agent in the development of cardiovascular dysfunction following protamine infusion. Many of the previous reports suggesting a cardiovascular depression by protamine were performed in the canine model, a species highly acceptable to these effects (13). Michaels and Barash failed to demonstrate any statistically significant changes in cardiac output, systemic blood pressure,

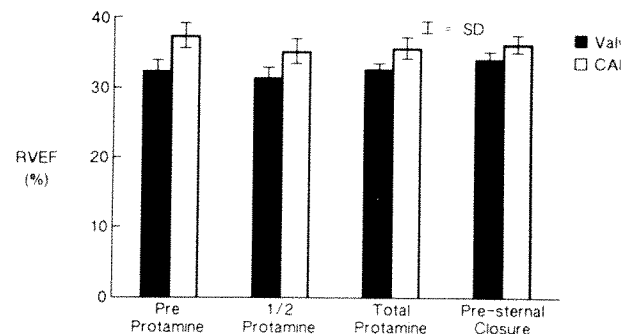


Figure 3. Right ventricular ejection fraction (RVEF) before, during, and after protamine administration.

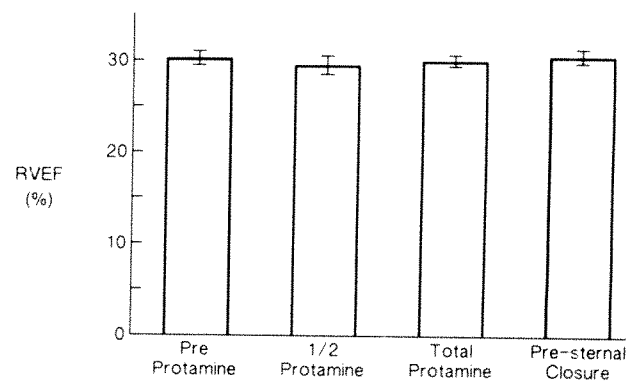


Figure 4. Right ventricular ejection fraction measurement in patients with pulmonary artery hypertension.

or vascular resistance when protamine was infused at rates of $0.5 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ or $1 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ in patients with good left ventricular function (2). In similar study, Conahan et al. (1) found no alteration in cardiac output when protamine was administered (3 mg/kg over 5 min) in patients following cardiac pulmonary bypass.

The liberation of histamine with subsequent systemic hypotension was proposed as a possible mechanism responsible for the hemodynamic instability observed following protamine administration (9). Casthely et al. evaluated the hemodynamic change associated with protamine infusion via the left atrium, the right atrium, or a peripheral vein. The greatest hemodynamic effects occurred when protamine was administered via the right atrium and least when administered via the peripheral vein. They postulate that the heparin-protamine complex formed when protamine is injected into the right atrium goes directly to the lung resulting in histamine release. When protamine is injected into the peripheral vein, the complex becomes diluted and histamine release may be prevented. In a further attempt to determine if the site of protamine injection was important in pre-

venting cardiovascular instability, Frater et al. measured the hemodynamics following right and left atrial injections of protamine (14). They failed to demonstrate any advantage of left side injection in preventing an anaphylactoid reaction. These data from the literature suggest that rate and dose of infusion, themselves, do not appear to be a reliable predictor in the development of RV failure following protamine infusion.

Prior exposure to protamine with the development of antiprotamine antibody has been implicated as a mechanism responsible for an adverse protamine reaction. Patients at risk would be those receiving protamine containing insulin preparations (NPH or protamine-zinc). Several isolated case reports of anaphylactoid response in this patient group have been published (15). However, convincing evidence demonstrating an immune-mediated basis (IgE or IgG) in patients who have suffered anaphylactoid reactions due to prior exposure to protamine containing insulin preparations is lacking. Proposed mechanisms include an immune-mediated response (15), IgG antibody to protamine (16), and complement consumption (11).

As a result of the incidence of protamine reaction occurring in patients with mitral valve disease reported by Lowenstein, it was speculated that underlying pulmonary vascular disease may predispose to protamine induced pulmonary artery vasoconstriction (3). These reactions may occur without documentation of previous exposure to protamine. The sequelae included pulmonary vasoconstriction and systemic hypotension immediately following protamine administration. The exact cause of this phenomenon has not been found. Redegran et al. have reported a similar hemodynamic picture associated with marked thrombocytopenia following protamine administration in a canine model (17). Although Bjoraker and Ketcham (18) demonstrated a decrease in mean blood pressure, no alterations in venous pressures were obtained following protamine administration even in patients where the patient count decreased to 72% of control levels. Thus, the precise etiology of pulmonary vasoconstriction remains unclear.

In conclusion, alterations in RV function are not a consistent consequence of protamine administration

following cardiopulmonary bypass. The precise factors responsible for the sporadic alterations in RV failure are unknown and may only become apparent when pulmonary hypertension is present.

References

1. Conahan TJ III, Andrews RW, MacVaugh H III. Cardiovascular effects of protamine sulfate in man. *Anesth Analg* 1981;60:33-6.
2. Michaels I, Barash PG. Hemodynamic changes during protamine administration. *Anesth Analg* 1983;62:831-5.
3. Lowenstein E, Johnson W, Lappas D, et al. Catastrophic pulmonary vasoconstriction associated with protamine reversal of heparin. *Anesthesiology* 1983;59:470-3.
4. Kay H, Afshari M, Barash P, et al. Measurement of ejection fraction by thermal dilution techniques. *J Surg Res* 1983;34:337-46.
5. Jardin F, Gueret P, Duborg O, et al. Right ventricular volumes: Thermolulution in the adult respiratory distress syndrome. *Chest* 1985;88:34-49.
6. Bull B, Huse W, Brauer F, Korpman R. Heparin therapy during extracorporeal circulation: The use of dose-response curve to individualize heparin and protamine dosage. *J Thorac Cardiovasc Surg* 1975;69:685-9.
7. Horrow J. Protamine: a review of its toxicity. *Anesth Analg* 1985;64:348-61.
8. Goldman BS, Joison J, Austen WG. Cardiovascular effects of protamine sulfate. *Ann Thorac Surgery* 1969;7:459-71.
9. Casthely P, Goodman K, Fyman P, et al. Hemodynamic changes after the administration of protamine. *Anesth Analg* 1986;65:78-80.
10. Jones RM, Hill AB. Effect of protamine or plasma ionized calcium in the dog. *Can Anaesth Soc J* 1982;29:65-7.
11. Stimler WP, Hojli TE, Bloor CM. Pulmonary injury induced by C3a and C5a anaphylatoxins. *Am J Pathol* 1980;100:327-41.
12. Chenoweth DE, Cooper BW, Hojli TE. Complement activation during cardiopulmonary activation during cardiopulmonary bypass: evidence for generation of C3a and C5a anaphylatoxins. *N Engl J Med* 1981;304:497-503.
13. Iwatsuki N, Matsukawa S, Iwatsuki K. A weak negative inotropic effect of protamine sulfate upon the isolated canine heart muscle. *Anesth Analg* 1980;59:100.
14. Frater RWM, Oka Y, Hong Y, et al. Protamine induced circulatory changes. *J Thorac Cardiovasc Surg* 1984;87:687-92.
15. Moorthy SS, Pond W, Rowland RG. Severe circulatory shock following protamine (an anaphylatic reaction). *Anesth Analg* 1980;59:77-8.
16. Doolan L, McKenzie I, Drafchef J, et al. Protamine sulfate hypersensitivity. *Anesth Intensive Care* 1981;9:47-9.
17. Radegran K, McAshlan C. Circulatory and ventilatory effects of induced platelet aggregation and their inhibition by acetylsalicylic acid. *Acta Anesthesiol Scand* 1972;16:76-84.
18. Bjoraker DG, Ketcham TR. In vivo platelet response to clinical protamine sulfate infusion. *Anesthesiology* 1982;57:A7.

Pulmonary Surfactant Films Affected by Solvent Vapors

Goran Enhorning, MD, Ralph Pototschnik, MD, Fred Possmayer, PhD, and Rosmarie Burgoyne, BSc

ENHORNING G, POTOTSCHNIK R, POSSMAYER F, BURGOWNE R. Pulmonary surfactant films affected by solvent vapors. *Anesth Analg* 1986;65:1275-80.

Pulmonary surfactant obtained from rabbit lung lavage was evaluated with the pulsating bubble surfactometer. Because surfactant forms a monomolecular film at the air-liquid interface consisting mainly of phospholipids, solvent vapors, which might be inhaled, could have a destructive influence on the surfactant monolayer. To assess the risk of such an inhalation, vapors from five solvents—halothane, chloroform, enflurane, acetone, and diethyl ether—were made to flow into the bubble of the surfactometer as it pulsated for 30 sec, i.e., during 10 pulsations. The vapors from halothane and chloroform, excellent solvents of dipalmitoyl-phosphatidylcholine (DPPC), had a destabilizing effect evidenced by the fact that surface tension at minimal bubble size increased from 0 to as high as 20 mN/m. When the

vapors were replaced with a flow of room air, the pressure tracing promptly returned to normal. The concentration of halothane vapor, however, had to be at least 20%, a concentration much higher than that used for anesthesia, to have a destabilizing effect on pulmonary surfactant. Twenty-five percent enflurane vapor had a less pronounced yet conspicuous impact. With 25% acetone and diethyl ether vapors, poor solvents of DPPC, surface tension at minimal bubble size remained unaffected. We conclude that vapors of halothane and chloroform, if inhaled in high concentration, might instantaneously obliterate the stabilizing effect of pulmonary surfactant but that anesthetic concentrations of halothane have no effect.

Key Words: LUNGS—pulmonary surfactant. ANESTHETICS, VOLATILE—halothane, diethyl ether, chloroform.

The amphipathic phospholipids of pulmonary surfactant are assumed to form a monomolecular film at the air-liquid interface of the finest branches of the lungs' airways, including the alveolar sacs (1,2). By reducing surface tension during expiration, this film inhibits alveolar collapse, and the stability obtained prevents development of atelectasis (3). This stabilizing ability, due to forces between the lipid molecules of the film, can be disrupted by adequate concentrations of certain lipid solvents. Some of these solvents, such as halothane, enflurane, and diethyl ether, vaporize relatively readily and are effective anesthetic agents. This makes it pertinent to examine the impact of a high concentration of such vapors on surfactant and to establish the lowest concentration that destabilizes a surfactant film. With this paper we report how we introduced the vapors from five different solvents, some of which are used as anesthetic agents,

into a pulsating bubble outlined with a film consisting of pulmonary surfactant.

Methods

Natural pulmonary surfactant was obtained by lavaging the lungs of young adult New Zealand rabbits. The technique is simple and has been used for several years (4). The animals were anesthetized with a slow intravenous (IV) injection of sodium pentobarbital and were bled to death by opening their carotid arteries and holding their heads low. The lungs were then lavaged with intratracheal saline using a standard intravenous bag held no higher than 40 cm above the lungs. When the fluid ceased to flow rapidly, the bag was disconnected, and the fluid ran out through the endotracheal tube, the end of which was no lower than 30 cm below the lungs. This procedure was repeated three times, and the lavage fluid obtained was centrifuged at $200 \times g$ for 5 min to remove cellular contamination and then at $1000 \times g$ and 4°C for 60 min. The second centrifugation yielded a white pellet which was resuspended in an equal volume of supernatant. This gave a natural surfactant preparation which was diluted 10 times in saline before use. I

Supported by Medical Research Council of Canada Grant MT-4497.

Received from the Departments of Obstetrics and Gynaecology, University of Toronto, Toronto, and University of Western Ontario, London, Ontario, Canada. Accepted for publication June 30, 1986.

Address correspondence to Dr. Enhorning, Children's Hospital, 219 Bryant Street, Buffalo, NY 14222.

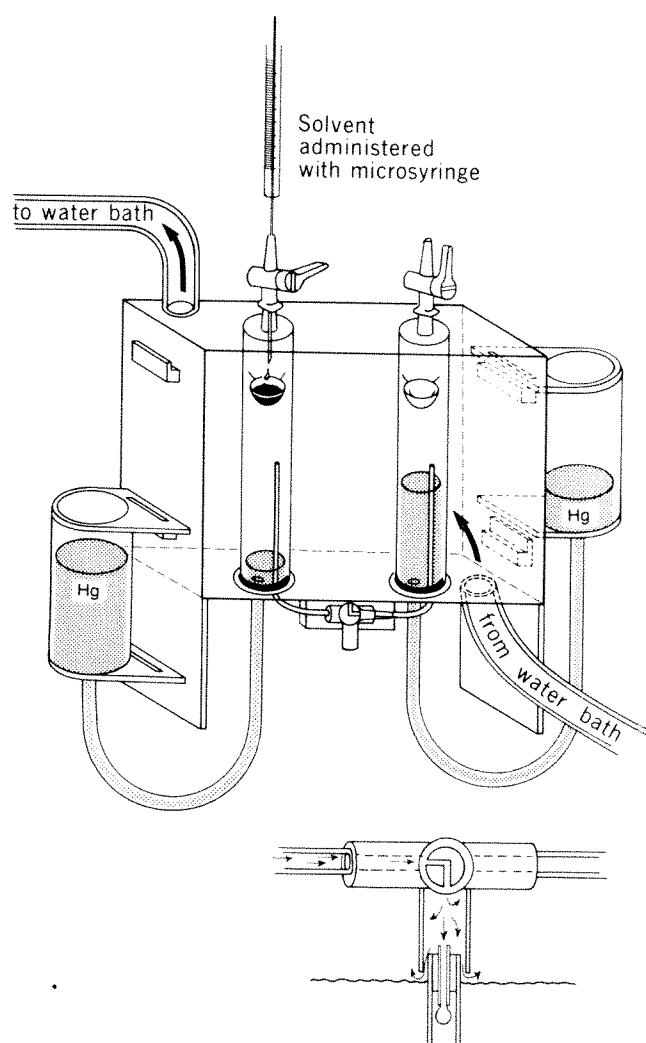


Figure 1. Solvent vapors were allowed to flow into the pulsating bubble with the arrangement shown. Two 30-ml glass syringes without plungers were enclosed in a temperature-controlled water bath. In each syringe was a glass cup for deposition of the solvent. The stopcock at top of syringe was opened momentarily after solvent evaporation. The mercury container outside the water bath was then raised, causing mercury to run into the syringe and build up a pressure of 50 torr. This forced the vapors from the left syringe to flow into the pulsating bubble when stopcock was in the position shown in detail at bottom of figure. After 10 cycles, stopcock was turned 90°, so that the flow of vapors from one syringe was replaced with that of air from the other.

then had a phospholipid concentration of approximately 2 mg/ml. A pulsating bubble surfactometer, a modification of the original method (5), was used for evaluation of surface properties. The principle is to record the pressure in the sample liquid surrounding a small bubble that, like an alveolus, communicates with ambient air. The bubble is pulsating at a rate of 20 cycles/min, so that its radius changes in a known pattern from a maximum of 0.55 mm to a minimum of 0.4 mm. From the law of Laplace, $\Delta P = 2\gamma/R$, the

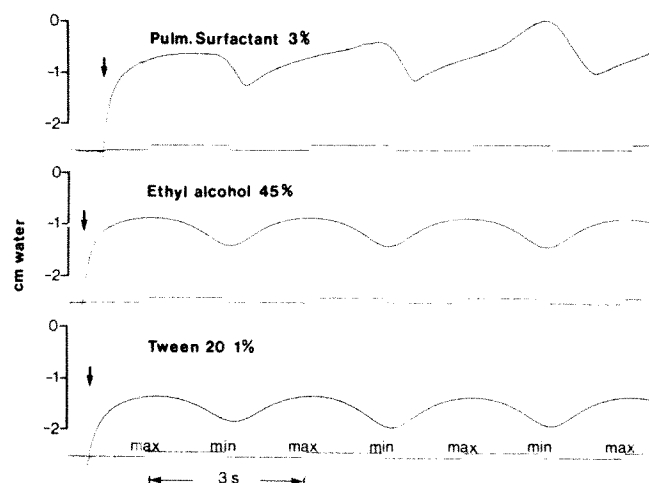
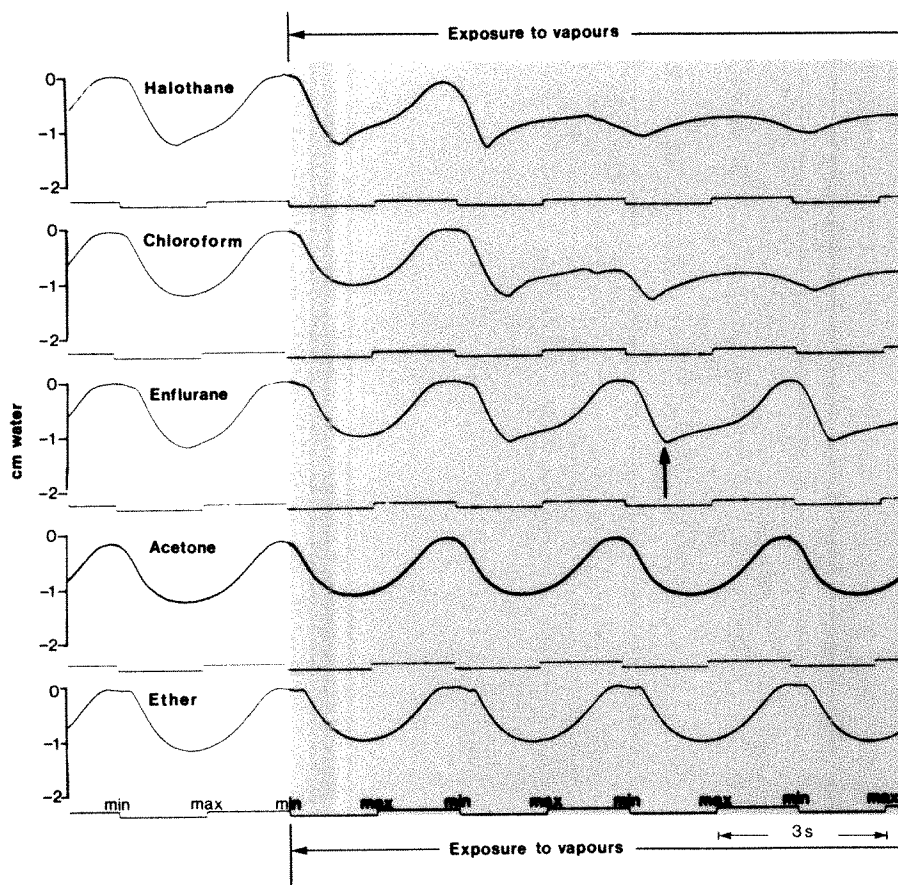


Figure 2. Tracings of pressure in liquids surrounding a pulsating bubble communicating with ambient air. The liquids, studied at 37°C, consist of a surfactant suspension obtained from the lung lavage of a young adult rabbit (top), ethyl alcohol (middle), and the detergent Tween 20 (bottom). The bubble radius changes from a maximum (max) of 0.55 mm to a minimum (min) of 0.4 mm in 1.5 sec. Arrows indicate initial expansion of bubble. The tracing with pulmonary surfactant in saline (30 mg phospholipids/ml) demonstrates that this material is immediately adsorbed to the air-liquid interface, reducing surface tension throughout the cycle to what can be calculated to be less than 35 mN/m. The same tracing demonstrates a changing surface tension that at end of third cycle reaches the value of zero at minimal bubble surface area. The other two tracings show changes in pressure as a result of changes in bubble radius and not in surface tension, calculated as 28 mN/m for ethyl alcohol and 37 mN/m for the detergent.

value of surface tension, γ , can be calculated, because the bubble radius, R , is known and the corresponding pressure gradient, ΔP , is recorded. The method has the advantages of being rapid and requiring a very small sample volume, 20 μ l. Furthermore, the disposable sample chamber is surrounded by water, the temperature of which is easily maintained at 37°C. The instrument was carefully calibrated, and three common liquids were studied: natural pulmonary surfactant suspension, 45% ethyl alcohol, and 1% Tween 20 solution.

The arrangement shown in Figure 1 was used for preparing solvent vapors of known temperature and concentration and causing them to flow into the pulsating bubble for a limited number of cycles, after which the vapors could be quickly replaced by another gas, e.g., air. The vapors of five solvents—halothane, chloroform, enflurane, acetone, and diethyl ether—were prepared at 37°C in concentrations calculated to be close to 25%. During precisely 10 cycles, i.e., 30 sec, they flowed into the pulsating bubble, the temperature of which was 37°C. At the end of the tenth cycle, the vapors were stopped from flowing into the bubble and were replaced with air. Because there was a very definite effect with halothane vapors

Figure 3. Twenty-five percent halothane and chloroform vapors quickly changed pressure tracings (for recovery phase, see Fig. 4). A similar concentration of enflurane had a moderate effect, consisting mainly of a break (arrow) during expansion phase. Twenty-five percent acetone and ether vapors did not alter the pressure tracing of an intact surfactant film.



at a concentration of 25%, halothane was also tested at other concentrations, the lowest being 2.5%.

Results

Figure 2 shows the pressure tracings obtained with pulmonary surfactant in the sample chamber and with two well-known, surface-active agents, ethyl alcohol and the detergent Tween 20. It can be seen and calculated that with pulmonary surfactant the surface tension changes with the pulsation and becomes close to zero at minimal bubble size, when the molecules in the surface monolayer are forced close together. They are hydrophobic, and energy would be required to make them leave the air-liquid interface of the surface monolayer and move into the surrounding liquid, the hypophase. With the other two surface-active agents, surface tension does not change appreciably during bubble pulsation, because the molecules reducing surface tension are not hydrophobic and will readily leave the surface and move into the hypophase. The surface area is then compressed as the bubble becomes smaller.

Twenty-five percent halothane and chloroform vapors had striking effects when they entered the bub-

ble outlined with pulmonary surfactant (Fig. 3). Almost immediately the pressure tracing changed, and after 2-4 pulsations had altered dramatically from one of pulmonary surfactant to that typical of a detergent. Surface tension was no longer alternating throughout the cycle but could be calculated to have a consistent value of approximately 20 mN/m.

The effect of 25% enflurane vapor was less dramatic, yet easy to recognize. When the vapors started to enter the bubble, two phenomena took place, first noticeable in the second cycle and clearly visible in the third. Pressure zero was no longer reached in a plateau, but only momentarily, and the pressure tracing developed a break (marked with an arrow in Fig. 3) while the bubble was increasing in size and its surface area expanding.

Twenty-five percent vapors of acetone and diethyl ether, poor solvents of disaturated phospholipids, had minimal effects on the pressure tracings and were unable to inhibit the cyclical change in bubble shape (Fig. 3).

It is important to note that when the strong vapors of halothane and chloroform were stopped from flowing into the bubble after 10 cycles, and were replaced with a flow of air, there was a rapid recovery, i.e., a

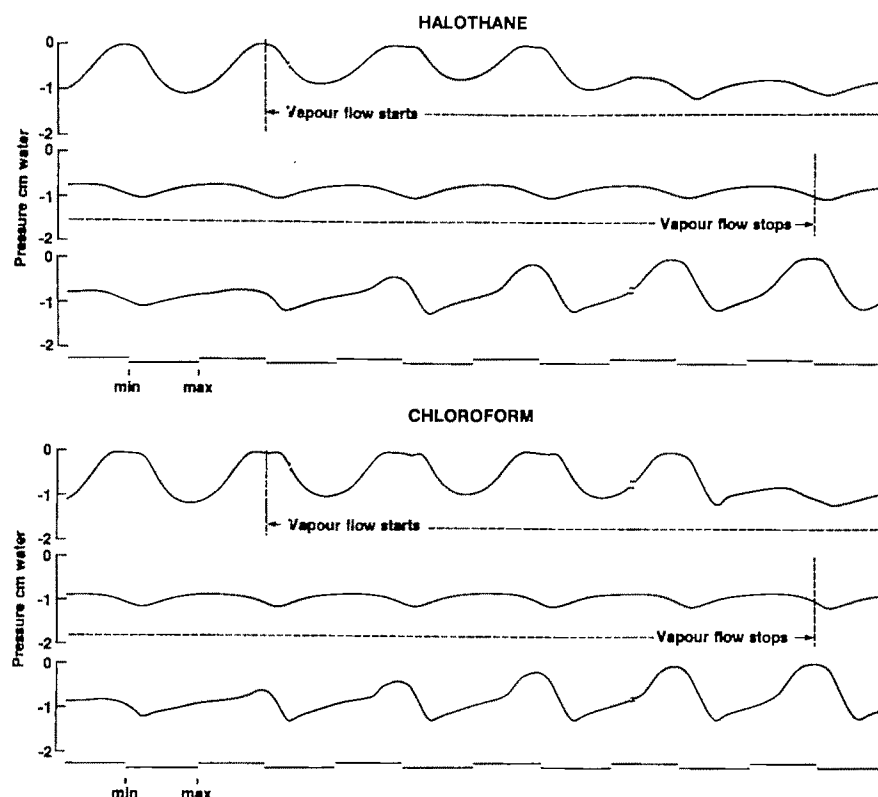


Figure 4. Twenty-five percent halothane or chloroform vapor flowing into the pulsating bubble quickly changed the pressure tracing to indicate a constant surface tension of 20 mN/m. When vapors were replaced with a flow of air, there was a rapid recovery.

return of the pressure tracing to the appearance it had before exposure to the vapors (Fig. 4).

The vapors of the halothane and chloroform had marked effects when they were flowing into the bubble at a concentration of 25%. The effect was still noticeable at 20%, but below this concentration there was no detectable destabilization. Because the stability index is similar for halothane and chloroform, it is only shown for halothane (Fig. 5).

Discussion

Pulmonary surfactant is difficult to define. Is it the material stored as lamellar bodies in the cytoplasm of the cells where it is synthesized in type II alveolar cells? Is it the tubular myelin, suspended in the alveolar hypophase, or the monomolecular film at the air-liquid interface of a pulsating bubble or an alveolus? Or is it simply DPPC with a 10% addition of a low molecular weight protein (5000 d) necessary for the fast formation of a monomolecular film, i.e., a fast adsorption rate (6)? Various attempts have been made to purify pulmonary surfactant, the most important based on density gradient centrifugation (7). We feel that a material called "natural surfactant" should be obtainable in a simple way from the airways, and without anything being added to it should be able to

quickly form a monomolecular film which, when compressed, will lower surface tension to close to zero. The "natural surfactant" we used for this study fulfilled those requirements and was the raw material for the preparation with which we successfully prevented the respiratory distress syndrome of preterm infants (8).

If surface tension were to remain at the same value throughout the respiratory cycle, and if that value were high, there would be a very definite risk that the smallest airways and alveoli would collapse as they approached their minimal size during expiration. This risk of instability can be appreciated by considering the law of Laplace, $\Delta P = 2\gamma/R$, which shows that the smaller the airway radius, R , the greater the transmural pressure, ΔP , required to counteract a surface tension, γ , which does not change. However, pulmonary surfactant has the important ability to influence surface tension, so that surface tension is changed and lowered with each breath, reaching an extremely low value as the film it forms at the air-liquid interface is being compressed to a minimal area during expiration. Surfactant thus prevents the development of atelectasis, a stabilizing effect first described and explained by Clements et al. (3). The concept can be appreciated with the bubble surfactometer. When pulmonary surfactant is being eval-

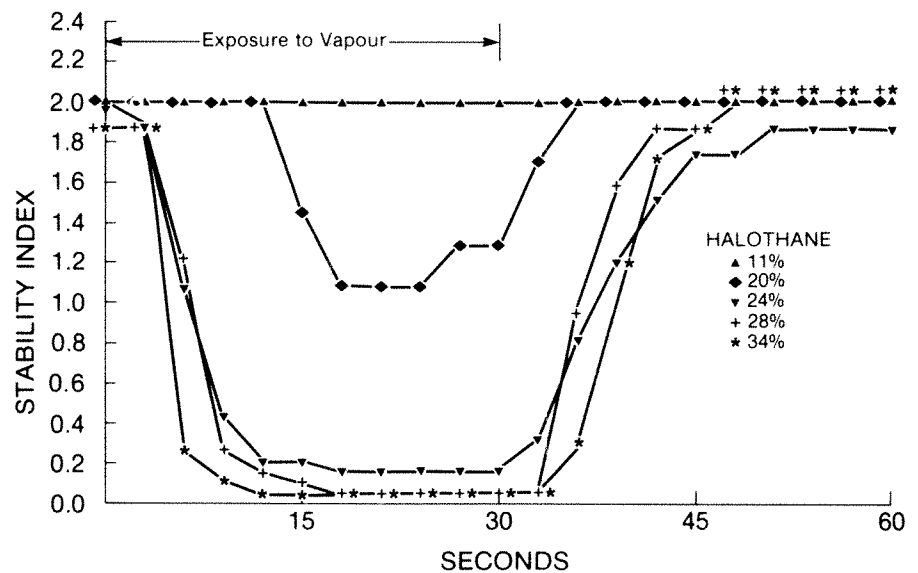


Figure 5. The effect on stability index, \bar{S} , calculated according to Clements et al. (3), $\bar{S} = 2(\gamma_{\max} - \gamma_{\min})/(\gamma_{\max} + \gamma_{\min})$, after exposure to halothane vapors of different concentrations. At 20% there clearly was destabilization, but not at 11%.

uated with this instrument it can be seen that the transmural pressure, ΔP , required to counteract the impact of surface tension increases during inspiration, but decreases during expiration (Figs. 2 and 3). In fact, the value of ΔP becomes zero well before the bubble has reached its smallest size and its surface area has been reduced by 50%. This implies that the reduction in surface area can be considerably less during breathing and yet surface tension will be brought down to a value approaching zero. Thus with the bubble surfactometer, surfactant is found to have a very obvious stabilizing effect. The recorded value is the pressure around the bubble and, knowing the bubble radius, surface tension can be calculated. A newer design of the surfactometer, now under construction, has a microcomputer, allowing continuous recordings of ΔP , surface tension or surface pressure.

When a bubble was pulsating in a solution of ethyl alcohol or the detergent Tween 20, the tracing was very different from that obtained with pulmonary surfactant (Fig. 2). These water-soluble, surface-active agents were unable to form a film able to lower surface tension to extremely low values at minimal bubble size. High concentrations of halothane and chloroform vapors quickly and completely removed the stabilizing ability of the surfactant film and, in principle, the tracing became similar to one obtained with ethyl alcohol or Tween 20. The "tidal volume," the change in size of the bubble as it pulsates, 0.43 mm^3 , became greater than the volume of air in the capillary of the sample chamber, 0.40 mm^3 . Thus as soon as the vapors started to flow out against the upper end of the capillary, they entered the bubble with the first pulsation and the effect was soon quite striking (Fig. 3).

The signs of a surfactant film, offering stability and resisting compression to a smaller area, were no longer apparent, and surface tension was not lowered to close to zero; instead, the tracing was similar to one obtained with a high concentration of ethyl alcohol, and surface tension throughout the cycle could be calculated to remain at a constant value of approximately 20 mN/m . When the strong vapors of halothane or chloroform were replaced with a flow of air, there was rapid recovery. Alveolar gas contains carbon dioxide, but we found that the presence or absence of this gas did not affect the tracing.

It should be noted that the most obvious destabilization was observed only with vapors of halothane and chloroform, and only when at concentrations of at least 25%. Because halothane vapors less than 20% had no noticeable impact, anesthetic machines ensuring a halothane concentration of no more than 4% offer a good margin of safety insofar as the potential detrimental effect on pulmonary surfactant is concerned. The safety of ether as anesthetic, even when used on an open mask, is well-documented and may be partly due to the inability of ether to affect pulmonary surfactant. Not even with the strongest concentrations did we notice a harmful effect.

Chloroform, like ether, is no longer used for anesthesia. However, the solvents studied are readily available in a laboratory, an industrial or domestic setting, and their vapors could be inhaled accidentally, or even intentionally. As reported by Fagan et al. (9), the immediate death after accidental inhalation of strong solvent vapors might have been due primarily to effects on the lungs rather than on the heart or central nervous system.

It can be correctly argued that because the vapor concentration will be considerably lower in the alveolus than in the inhaled air, damage to the alveolar surfactant is not to be expected. However, an effect to the surfactant film that could be dangerous, or even lethal, can be conceived to occur not in the alveolus but in the respiratory bronchiole. There the vapor concentration is higher than in the alveolus at end of inspiration, and during expiration surface tension can be expected to become excessive to what it is in the alveolus. The law of Laplace for a spherical surface, as in the alveolus, is $P = 2\gamma/R$, and for a cylindrical surface, as in the respiratory bronchiole, is $P = \gamma/R$. Therefore, provided that the radius of curvature, R , has half the value in the respiratory bronchiole as in the alveolus and that surface tension, γ , is the same in the two airway sections, they would require the same pressure, P , to counteract the collapsing effect of surface tension. However, if the respiratory bronchiole is narrow, with a radius less than half of what it is in the alveolus, and/or its surface tension has suddenly been raised after inhalation of very high concentrations of halothane or chloroform, then the respiratory bronchiole, and not the alveolus, is the most likely site of a collapse. Massive air trapping would then result and, because atelectasis would not develop initially, the autopsy findings would be minimal.

The immediate and marked effects of halothane and chloroform vapors can be explained by the phospholipids in the surfactant monolayer becoming completely dissolved. The lipid solution probably stayed at the surface of the bubble, because the pressure tracing of a normal surfactant film returned almost instantaneously as air replaced the solvent vapors. The impact was less pronounced with enflurane, probably because it is a weaker solvent. In principle, though, enflurane vapors acted similarly to those of halothane and chloroform, but the effect was far less marked. It was noticeable, however, during expansion, when a sudden kink in the pressure tracing (the arrow in Fig. 3) indicated that the intermolecular forces had become so weakened that they were no longer able to maintain the intactness of the expanding film. Instead, "cracks" formed in the film, which during approximately half the cycle allowed the appearance of the pressure tracing caused by surface tension of the surrounding liquid. As the bubble diminished in size, the "cracks" closed again and the tracing returned to that of a normal surfactant film at the air-liquid interface.

Twenty-five percent acetone and diethyl ether vapors had no discernible impact on pulmonary surfactant, which can be explained by the inability of these solvents to dissolve disaturated phospholipids. At low temperatures the poor solubilizing action of acetone has been used to concentrate the disaturated, and hence surface-active, phospholipids. Disaturated phospholipids are precipitated in cold acetone when the lecithin to sphingomyelin ratio (L/S ratio) is determined as a way of assessing the fetal lung maturity (10). It is especially the lipids with low surface activity that are dissolved and removed with acetone. It has been suggested (2,11,12) that the molecules forming the final monolayer at the air-liquid interfaces of the lung are mainly disaturated and perhaps consist almost entirely of DPPC. Our observation that high concentrations of halothane and chloroform vapors were obviously destabilizing, whereas similar concentrations of acetone and diethyl ether had no disturbing effect on the surfactant film, is compatible with that theory.

References

- Goerke J. Lung surfactant. *Biochim Biophys Acta* 1974;344:241-61.
- Scarpelli EM. *The Surfactant System of the Lung*. Philadelphia: Lea and Febiger, 1968.
- Clements JA, Hustead RF, Johnson PP, Gribetz I. Pulmonary surface tension and alveolar stability. *J Appl Physiol* 1961; 16:444-50.
- Enhoring G, Robertson B. Lung expansion in the premature rabbit fetus after tracheal deposition of surfactant. *Pediatrics* 1972;50:58-66.
- Enhoring G. A pulsating bubble technique for evaluating pulmonary surfactant. *J Appl Physiol* 1977;43:198-203.
- Takahashi A, Fujiwara T. Proteolipid in bovine lung surfactant: its role in surfactant function. *Biochem Biophys Res Commun* 1986;135:527-32.
- King RJ, Clements JA. Surface active materials from dog lung. I. Method of isolation. *Am J Physiol* 1972;223:707-14.
- Enhoring G, Shennan A, Possmayer F, Dunn M, Chen CP, Milligan J. Prevention of neonatal respiratory distress syndrome by tracheal instillation of surfactant: a randomized clinical trial. *Pediatrics* 1985;76:145-53.
- Fagan DG, Forrest JB, Enhoring G, Lamprey M, Guy J. Acute pulmonary toxicity of a commercial fluorocarbon-lipid aerosol. *Histopathology* 1977;1:209-23.
- Gluck L, Kulovich MV. Lecithin/sphingomyelin ratios in amniotic fluid in normal and abnormal pregnancies. *Am J Obstet Gynecol* 1973;115:539-46.
- Watkins JC. The surface properties of pure phospholipids in relation to those of lung extracts. *Biochim Biophys Acta* 1968;152:293-306.
- Notter RH, Tabak SA, Mavis RD. Surface properties of binary mixtures of some pulmonary surfactant components. *J Lipid Res* 1980;21:10-22.

Epidural Anesthesia with Lidocaine and Bupivacaine: Effects of Epinephrine on the Plasma Concentration Profiles

Anton G. L. Burm, PhD, Jack W. van Kleef, MD, PhD, Marina P. R. R. Gladines, Geert Olthof, MD, and Johan Spierdijk, MD, PhD, FFARCS

BURM AGL, VAN KLEEF JW, GLADINES MPRR, OLTHOF G, SPIERDIJK J. Epidural anesthesia with lidocaine and bupivacaine: effects of epinephrine on the plasma concentration profiles. *Anesth Analg* 1986;65:1281-4.

The effects of epinephrine on the plasma concentrations and derived pharmacokinetic parameters were studied after epidural administration of lidocaine and bupivacaine. Addition of epinephrine to the local anesthetic solutions reduced the mean peak plasma concentrations of lidocaine and bupiva-

caine from 2.2 to 1.7 $\mu\text{g/ml}$ (23%) and from 0.73 to 0.53 $\mu\text{g/ml}$ (28%), respectively, but did not alter the times at which the peak concentrations were reached. Epinephrine also did not alter the terminal half-lives or the total plasma clearances. The results suggest that addition of epinephrine to minimize plasma concentrations is as relevant with bupivacaine as it is with lidocaine.

Key Words: ANESTHETIC TECHNIQUES, EPIDURAL. ANESTHETICS, LOCAL—lidocaine, bupivacaine. PHARMACOKINETICS—lidocaine, bupivacaine.

Epinephrine is commonly added to local anesthetic solutions for epidural administration to improve the quality and prolong the duration of the epidural block, as well as to reduce the potential for systemic toxicity after absorption of the local anesthetic into the general circulation. It is generally assumed that epinephrine decreases the local blood flow, thereby slowing the systemic absorption and increasing the neuronal uptake of the local anesthetic agent (1,2). The possible contribution of a direct pharmacologic action of epinephrine (3,4) on spinal nerve structures remains to be clarified.

Addition of epinephrine to lidocaine solutions reduced the peak plasma concentrations of lidocaine after epidural administration consistently by about 30–40% (5–7). However, the corresponding reduction obtained with bupivacaine solutions varied from 5–25% (8–11). As far as protection against systemic toxicity is concerned, the impact of the addition of epinephrine to bupivacaine solutions is not clear. We have therefore reexamined the effects of addition of epinephrine to bupivacaine solutions on the plasma con-

centrations and some derived pharmacokinetic parameters. Lidocaine was included in the study as a reference because the effects of addition of epinephrine are well-documented.

Methods

Forty healthy (ASA status I) patients, between 20 and 50 yr old and scheduled for minor general or orthopedic surgery of the lower limbs or for minor urologic operations, participated in the investigation. The study was approved by the Committee on Medical Ethics of the University Hospital and informed consent was obtained from each patient.

The local anesthetic solutions studied were 2% lidocaine and 0.5% bupivacaine. To 20 ml of the local anesthetic solution 0.1 ml of a 1:1000 epinephrine solution was freshly added, giving a final concentration of 5 $\mu\text{g/ml}$ (1:200,000) epinephrine. Addition or omission of epinephrine was randomized. The local anesthetic test solutions (3 ml), which were used to detect an inadvertent intravascular localization of the tip of the epidural needle, always contained 5 $\mu\text{g/ml}$ epinephrine.

Anesthetic Procedure

The patients were premedicated with lorazepam, 2 mg sublingually, about 1.5 hr, and atropine, 0.5 mg

Supported by Astra Pharmaceutica, Rijswijk, The Netherlands. Received from the Department of Anesthesiology, University Hospital, Leiden, The Netherlands. Accepted for publication July 24, 1986.

Address correspondence to Dr. Burm, Department of Anesthesiology, University Hospital, PO Box 9600, 2300 RC Leiden, The Netherlands.

Table 1. Mean Age, Body Weight, Height and Male/Female Ratio for Each Group of Patients^a

	Lidocaine plain (n = 10)	Lidocaine plus epinephrine (n = 10)	Bupivacaine plain (n = 10)	Bupivacaine plus epinephrine (n = 10)
Age (yr)	34 ± 8	33 ± 10	32 ± 8	31 ± 7
Body weight (kg)	79 ± 13	82 ± 14	81 ± 9	76 ± 14
Height (cm)	179 ± 11	179 ± 9	177 ± 4	177 ± 13
Male/Female ratio	7/3	7/3	7/3	6/4

^aValues are means ± SD, where appropriate.

intramuscularly, about 0.5 hr before the epidural procedure. A central venous catheter was introduced into the basilic or the cephalic vein in the contralateral arm after local infiltration. The catheter was advanced until the tip was located in the central conduit, but at least 6 cm proximal to the junction of the azygos vein and the superior vena cava. The correct location of the tip of the catheter was verified using roentgenograms of the thorax. Lumbar puncture was performed with the patient sitting. After local infiltration of the skin an epidural Tuohy needle was inserted via the third lumbar vertebral interspace. The agent used for infiltration of the arm and the back (lidocaine or bupivacaine) was never the same as the one to be studied. The epidural space was identified by the loss of resistance technique. Once the needle was placed into the epidural space, 3 ml of the test solution were injected. Two to three minutes later 20 ml of the solution to be investigated were injected at a rate of 1 ml/sec. Immediately after the injection the patient was asked to assume a supine position. During the operation the patient remained supine on the operating table, which was kept horizontal. Sedative drugs were not administered. When necessary, postoperative pain was controlled with methadone or paracetamol.

The level of analgesia was assessed using pin-pricks, and the degree of motor block was determined using a modified Bromage classification. Both assessments were made bilaterally by an independent investigator, who, along with the patient, was unaware of whether or not epinephrine had been added to the local anesthetic solution.

Pharmacokinetic Investigations

Central venous blood samples were collected before the epidural injection, at 5-min intervals during the first 30 min, and from then on at intervals gradually increasing from 10 min to 4 hr until 24 hr after the injection. Blood samples were transferred into heparinized centrifuge tubes. After centrifugation, plasma was collected and stored at -20°C. Local anesthetic

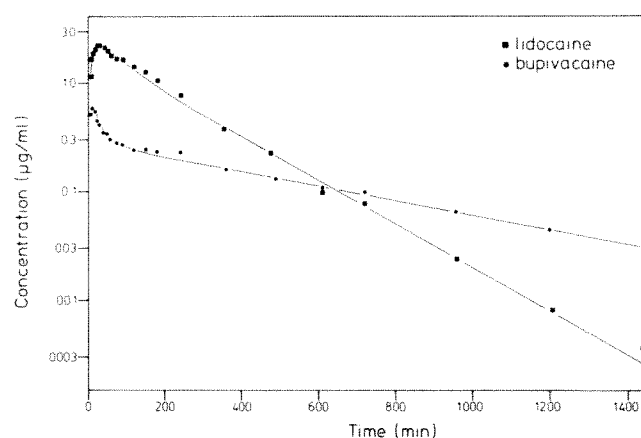


Figure 1. Typical plasma concentration curves, obtained after epidural administration of plain 2% lidocaine (460 mg dose) and 0.5% bupivacaine (115 mg dose) solutions to two different patients.

concentrations were determined using capillary gas chromatography, according to procedures described elsewhere (12,13) with a few modifications (14). The individual peak plasma concentrations (C_{max}) and the corresponding peak times (t_{max}) were determined. Terminal half-lives ($t_{1/2,z}$) were calculated from the rate constants (k_z) obtained by linear regression analysis of the log-linear part of the plasma concentration-time curve: $t_{1/2,z} = 0.69/k_z$. The area under the plasma concentration-time curve (AUC) was calculated using the linear trapezoidal rule, including extrapolation to infinity (15). The total plasma clearance (CL) was calculated with the following equation: $CL = D/AUC$, where D is the administered dose.

Statistical Analysis

All data are presented as mean ± standard deviation, where appropriate. In order to test the effects of epinephrine a two sample *t*-test was used. A Fisher exact test was used to compare proportions. A value of $P < 0.05$ was regarded as the minimum level of significance.

Table 2. Pharmacokinetic Data after Epidural Injection of 2% Lidocaine and 0.5% Bupivacaine Solutions

	Lidocaine plain (n = 10)	Lidocaine plus epinephrine (n = 10)	Bupivacaine plain (n = 10)	Bupivacaine plus epinephrine (n = 10)
t _{max} (min)	27 ± 12	32 ± 11	19 ± 8	21 ± 8
C _{max} (μg/ml)	2.2 ± 0.2 ^a	1.7 ± 0.3 ^a	0.73 ± 0.30 ^b	0.53 ± 0.13 ^b
t _{1/2} (min)	189 ± 42	197 ± 50	377 ± 62	466 ± 154
Clearance (ml/min)	902 ± 111	897 ± 179	525 ± 161	538 ± 160

Values are means ± SD.

Abbreviations: t_{max}, time of peak plasma concentration; C_{max}, peak plasma concentration; t_{1/2}, terminal half-lives.

^aDifference between lidocaine plain and lidocaine plus epinephrine: *P* < 0.0005.

^bDifference between bupivacaine plain and bupivacaine plus epinephrine: *P* < 0.05.

Results

There were no significant differences in age, body weight, height, and ratio of females to males between the groups of patients who received a local anesthetic solution with epinephrine and those who received a plain solution (Table 1).

Epinephrine did not alter the onset of analgesia or the attained analgesia levels, which were around T-8 with both lidocaine solutions and around T-7 and T-8 with the plain and the epinephrine-containing bupivacaine solutions, respectively. Addition of epinephrine resulted in a moderate prolongation of the duration of the epidural block after administration of lidocaine. With bupivacaine solutions a prolongation of the duration was obtained in the lower segments only. Full details of the effects of epinephrine on the onset, the quality, and the duration of the epidural block have been described elsewhere (14).

Typical plasma concentration curves showing the general characteristics after epidural administration of lidocaine and bupivacaine are given in Figure 1. The derived pharmacokinetic parameters are presented in Table 2.

Peak plasma concentrations obtained with epinephrine-containing solutions of both lidocaine and bupivacaine were lower than those obtained with the plain solutions. Addition of epinephrine decreased the mean peak concentrations of lidocaine from 2.2 μg/ml to 1.7 μg/ml (*P* < 0.0005), and the mean peak concentrations of bupivacaine from 0.73 μg/ml to 0.53 μg/ml (*P* < 0.05). These decreases in the peak concentrations were not accompanied by changes in the times to peak levels. The terminal half-life of lidocaine (mean value 189 min) was not affected by addition of epinephrine (197 min). The terminal half-life of bupivacaine also did not differ between epinephrine-containing solutions (466 min) and plain solutions (377 min). The mean values for the clearances of lidocaine and bupivacaine were approximately 900 and 530 ml/min, respectively, and were not affected by the addition of epinephrine.

Discussion

It is generally assumed that the effects of addition of epinephrine to bupivacaine solutions are not as marked as the effects of its addition to lidocaine solutions. This assumption may be true as far as the effects on the quality and the duration of the epidural block are concerned (16-20). However, this finding does not imply that the effects of epinephrine on the plasma concentrations also differ. In this study epinephrine reduced peak plasma concentrations of both lidocaine and bupivacaine to a similar extent (approximately 25%). This value may slightly underestimate the effect of epinephrine, because the patients receiving a plain local anesthetic solution also received a test solution with epinephrine, which was done to detect a possible inadvertent intravascular location of the tip of the epidural needle. Had we omitted epinephrine from the test solutions, the peak plasma concentrations in the patients receiving a plain solution might have been somewhat higher.

The plasma concentration profiles we observed are consistent with the biphasic absorption of lidocaine and bupivacaine, as described by Tucker and Mather (2,21) and by Burm (14). Taking into consideration the rapid distribution and elimination of lidocaine and bupivacaine (2,14,21), the rapid absorption phase explains the rapid increase in plasma concentrations and the short peak times. The slow absorption phase is reflected in the terminal part of the plasma concentration curves. The terminal half-lives of lidocaine and bupivacaine appear to be longer after epidural than after intravenous administration. This difference is not due to differences in the disposition of the local anesthetics after epidural and intravenous administration (14), but to the fact that the continuing absorption rate-limits the decay of the plasma concentrations after epidural administration. In fact, the terminal half-life of bupivacaine appears to be similar to the absorption half-life, which characterizes the slow absorption phase of bupivacaine (2,14,21).

The effects of epinephrine on the absorption ki-

netics of local anesthetics have also been studied by Tucker and Mather (2,21). In their study epinephrine reduced the fraction of the dose absorbed in the fast phase by approximately 40%, irrespective of the local anesthetic used (lidocaine or etidocaine). Assuming that this reduction holds for bupivacaine this explains why the peak plasma concentrations of lidocaine and bupivacaine were reduced to a similar extent in this study. The fact that the peak times and the terminal half-lives were not altered by the addition of epinephrine is also consistent with the observation of Tucker and Mather (2,21) that addition of epinephrine does not alter the absorption rate constants.

Interpretations of the effects of epinephrine on the plasma concentration profiles of local anesthetics after epidural administration assume that epinephrine does not alter the disposition of the local anesthetics. Unfortunately, data to validate this assumption are lacking. Therefore we also determined the influence of epinephrine on the total plasma clearance. In doing so it was assumed that the administered dose is fully absorbed intact into the general circulation. This assumption has been recently validated (14). In this study we could not demonstrate an effect of epinephrine on the clearance, although slight transient effects may have remained undetected.

The results of this study demonstrate that addition of epinephrine reduces the peak plasma concentrations of bupivacaine and lidocaine to a similar extent. Therefore addition of epinephrine to minimize the peak plasma concentrations and therefore the potential for systemic toxicity, may be as relevant with bupivacaine as it is with lidocaine.

The authors thank Mrs. M. de Beer and Mr. M. L. Bolt for their assistance with the clinical investigations and Mrs. M. P. M. Toelen for typing the manuscript.

References

1. Bromage PR. Epidural analgesia. 1st ed. Philadelphia: W.B. Saunders Company, 1978:85-6,142-7,284-7.
2. Tucker GT, Mather LE. Clinical pharmacokinetics of local anesthetics. *Clin Pharmacokinet* 1979;4:241-78.
3. Collins JG, Kitahata LM, Homma E, Suzukawa M. Spinal cord effects of epinephrine. *Anesth Analg* 1981;60:913-4.
4. Kraynack BJ, Gintautas J, Tjaj H. Local anesthetic action of epinephrine and ephedrine. *Regional Anesthesia* 1983;8:32-3.
5. Braid DP, Scott DB. The systemic absorption of local analgesic drugs. *Br J Anaesth* 1965;37:394-404.
6. Scott DB, Jebson PJR, Braid DP, Ortengren B, Frisch P. Factors affecting plasma levels of lignocaine and prilocaine. *Br J Anaesth* 1972;44:1040-9.
7. Mather LE, Tucker GT, Murphy TM, Stanton-Hicks MdA, Bonica JJ. The effects of adding adrenaline to etidocaine and lignocaine in extradural anaesthesia II: pharmacokinetics. *Br J Anaesth* 1976;48:989-94.
8. Wilkinson GR, Lund PC. Bupivacaine levels in plasma and cerebrospinal fluid following peridural administration. *Anesthesiology* 1970;33:482-6.
9. Appleyard TN, Witt A, Atkinson RE, Nicholas ADG. Bupivacaine carbonate and bupivacaine hydrochloride: a comparison of blood concentrations during epidural blockade for vaginal surgery. *Br J Anaesth* 1974;46:530-3.
10. Abdel-Salam AR, Vonwiller JB, Scott DB. Evaluation of etidocaine in extradural block. *Br J Anaesth* 1975;47:1081-6.
11. Reynolds F, Taylor G. Plasma concentrations of bupivacaine during continuous epidural analgesia in labour: the effect of adrenaline. *Br J Anaesth* 1971;43:436-40.
12. De Boer AG, Breimer DD, Mattie H, Pronk J, Gubbens-Stibbe JM. Rectal bioavailability of lidocaine in man: partial avoidance of "first pass" metabolism. *Clin Pharmacol Ther* 1979;26:701-9.
13. Burm AGL, Van Kleef JW, De Boer AG. Gas chromatographic determination of bupivacaine in plasma using a support coated open tubular column and a nitrogen-selective detector. *Anesthesiology* 1982;57:527-9.
14. Burm AGL. Pharmacokinetics and clinical effects of lidocaine and bupivacaine following epidural and subarachnoid administration in man (PhD Thesis). Leiden, The Netherlands: University of Leiden, 1985. 187 pp.
15. Rowland M, Tozer TN. Clinical pharmacokinetics: concepts and applications. 1st ed. Philadelphia: Lea and Febiger, 1980:288-90.
16. Murphy TM, Mather LE, Stanton-Hicks MdA, Bonica JJ, Tucker GT. The effects of adding adrenaline to etidocaine and lignocaine in extradural anaesthesia I: block characteristics and cardiovascular effects. *Br J Anaesth* 1976;48:893-7.
17. Löfström B, Green K, Jonsson O, McCarthy G. An evaluation of bupivacaine (Marcaine®) without adrenaline. *Acta Anaesthesiol Scand* 1970;Suppl 37:282-5.
18. Waters HR, Rosen N, Perkins DH. Extradural blockade with bupivacaine: a double blind trial of bupivacaine with adrenaline 1/200,000, and bupivacaine plain. *Anaesthesia* 1970;25:184-90.
19. Moore DC, Bridenbaugh LD, Bridenbaugh PO, Thompson GE. Bupivacaine hydrochloride: a summary of investigational use in 3274 cases. *Anesth Analg* 1971;50:856-72.
20. Sinclair CJ, Scott DB. Double-blind comparison of 0.75% bupivacaine and 1.5% etidocaine with and without epinephrine in epidural block. *Regional Anesthesia* 1982;7:77-8.
21. Tucker GT, Mather LE. Pharmacokinetics of local anaesthetic agents. *Br J Anaesth* 1975;47:213-24.

Comparison of the Effects of Atropine and Glycopyrrolate on Pulmonary Mechanics in Patients Undergoing Fiberoptic Bronchoscopy

Jonathan R. Thorburn, FFA(SA), Michael F. M. James, FFARCS, Charles Feldman, FCP(SA), Donald G. Moyes, FFARCS, and Pierre S. Du Toit, BSc

THORBURN JR, JAMES MFM, FELDMAN C, MOYES DG, DU TOIT PS. Comparison of the effects of atropine and glycopyrrolate on pulmonary mechanics in patients undergoing fiberoptic bronchoscopy. *Anesth Analg* 1986;65:1285-9.

The effects of atropine and glycopyrrolate on forced vital capacity (FVC), forced expired volume in one second (FEV₁), the FEV₁/FVC ratio, and peak expiratory flow (PEF) were compared in 44 patients undergoing fiberoptic bronchoscopy under general anesthesia. Both anticholinergic agents im-

proved pulmonary function equally before general anesthesia, but in both groups there was a small and again equal deterioration in pulmonary function after the procedure. The protective effects of the two drugs were not significantly different. Because of the lower incidence of undesirable side effects, glycopyrrolate is recommended as the anticholinergic agent of choice for bronchoscopy.

Key Words: PARASYMPATHETIC NERVOUS SYSTEM—atropine, glycopyrrolate. LUNG—blood flow.

In patients undergoing instrumentation of the major airways by means of rigid, and more recently, fiberoptic bronchoscopes (1), atropine is frequently used as a premedication with both general or topical anesthesia (2-6) to reduce bronchial secretions and prevent bradycardia (7,8), as well as to protect against the deleterious effects of the instrumentation on pulmonary mechanics (3,9,10). Glycopyrrolate appears to have certain advantages over atropine for patients undergoing bronchoscopy, because it causes fewer systemic disturbances and because of its superior action in reducing bronchial secretions. If the effects of atropine and glycopyrrolate on pulmonary function are similar, then it would be preferable to use glycopyrrolate, but the effects of glycopyrrolate on pulmonary mechanics in patients with abnormal lung function or during pulmonary instrumentation have not been studied. Thus, we decided to study patients scheduled for fiberoptic bronchoscopy under general anesthesia to determine the effects of atropine and glycopyrrolate on preoperative and postoperative lung

function when used for both premedication and at the time of reversal of neuromuscular blockade.

Methods

Informed, written consent was obtained from patients scheduled for fiberoptic bronchoscopy who were physically and mentally able to perform pulmonary function tests. Patients who were pregnant and ASA class IV patients were excluded. Patients were assigned alternately to receive either atropine (group A) or glycopyrrolate (group G). A Cavitron Spirometric Computer Model SC-20A (Cavitron Cardiopulmonary Computer, Cavitron International, Anaheim, California) was used for the performance of all pulmonary function tests, which were conducted with the patient sitting. This instrument constructs a flow-volume loop from which forced vital capacity (FVC) is determined, and from the FVC forced expiratory volume in 1 sec (FEV₁), the FEV₁/FVC ratio, and peak expiratory flow (PEF) were mathematically derived. Three flow-volume loops were obtained from all subjects before the administration of any premedicant drugs. The flow-volume loop with the best FVC and PEF was selected on this and each subsequent test. After successful completion of initial pulmonary function tests (predrug), group A patients received 1 mg atropine sulfate and group G patients received 0.5 mg glyco-

Received from the Departments of Anaesthesia, Medicine, and Statistics, University of the Witwatersrand, Johannesburg, South Africa. Accepted for publication July 3, 1986.

Address correspondence to Dr. Thorburn, Department of Anaesthesia, University of Witwatersrand, Johannesburg 2000, South Africa.

pyrrolate, both intravenously. Thirty minutes later a second set of pulmonary function tests were performed (postdrug).

After the second series of pulmonary function tests, the patients had electrocardiograph leads attached to the chest wall, and a blood pressure cuff was applied to the left upper arm. The patients were preoxygenated with 100% oxygen for 3 min and given 0.5 mg pancuronium intravenously to attenuate the fasciculations caused by succinylcholine, followed by a sleep dose of 2.5% thiopental. Ventilation was manually assisted with a mixture of 50% oxygen in nitrous oxide using a face mask and a Mapleson D coaxial (Bain) (11,12) system. Once adequate ventilation of the lungs was ensured, succinylcholine 1 mg/kg was given intravenously, and laryngoscopy and tracheal intubation were performed when relaxation was complete. Using the Bain system, the lungs were manually ventilated with 50% oxygen in nitrous oxide plus halothane, 0.5–1% as required to maintain a satisfactory depth of anesthesia. After recovery from succinylcholine paralysis, 4 mg pancuronium was administered to maintain muscular relaxation.

Fiberoptic bronchoscopy was performed through the endotracheal tube and brushings and/or biopsy specimens were taken in all cases. During bronchoscopy fresh gas flows were increased to 16 L/min to compensate for the inevitable leaks that occurred around the bronchoscope. At the end of the procedure, muscular paralysis was reversed with neostigmine, 2.5 mg, given simultaneously with either atropine, 1 mg, or glycopyrrolate, 0.5 mg, intravenously. Once satisfactory spontaneous ventilation was established and the patient was able to obey commands, final tracheal suction was performed and the endotracheal tube was removed. After satisfactory recovery the patient was returned to the ward. Two and one-half hours after extubation, a third series of pulmonary function tests were performed (end-test).

Statistical analysis had to take into account the general pattern of reaction to the drugs, namely, an increase in pulmonary ventilation in the approximately 30 min between predrug and postdrug measurements and the decrease in pulmonary ventilation over the 3 hr between postdrug and end-test measurements. A parabolic or quadratic curve was fitted to the three points given by the responses of each patient at predrug, postdrug, and end-test measurements. The quadratic effect, which is calculated from the orthogonal polynomial, gives an estimate of the curvature of the three points and hence measures the overall pattern of response to both drugs. A second type of comparison was made by considering the gradients from predrug to postdrug, from postdrug to end-test,

and from predrug to end-test as separate responses that measure the effects of the drugs in the two different situations prevailing before and after bronchoscopy. Comparisons between the atropine and glycopyrrolate groups were made using Student's *t*-test. Comparison between predrug, postdrug, and end-test means within each group were made using Student's method of paired differences and hence have a much lower SE. Significance was defined as $P < 0.05$.

Results

The 44 patients were allocated equally to each group at random. This random process resulted in group A having three females and 19 males with an average age of 52.0 ± 2.2 yr and group G having five females and 17 males also with an average age of 52.0 ± 2.6 yr. The differences in sex distribution and age between the groups were not statistically significant. The predrug pulmonary function measurements were higher on average in group G, but this difference was not significant. The predrug readings were significantly lower than predicted values: the FVC was $54.4 \pm 1.8\%$ of predicted values and the FEV₁ was $47.2 \pm 3.01\%$ of predicted values. Only one of the 44 patients had predrug results greater than 90% of predicted values.

The means of the 4 responses (FVC, FEV₁, FEV₁/FVC, and PFL) are shown in Table 1 for each group and for each test. The means of the gradients and the quadratic effects are also shown. The standard error of the mean is given in each case.

In comparing predrug with postdrug measurements, both anticholinergic agents produced statistically significant improvements in FEV₁, FEV₁/FVC, and PFL. Forced vital capacity increased significantly in group A, but not in group G. Intergroup comparisons showed no significant differences in any of the measured postdrug values except PFL, where the postglycopyrrolate mean of 5.79 ± 0.35 was significantly higher than the postatropine mean of 4.66 ± 0.36 .

After bronchoscopy, PFL and FVC decreased significantly in both groups when initial predrug and end-test values were compared, and when postdrug and end-test results were compared. The forced expiratory volume in one second decreased significantly below postdrug values in both groups at end-test. In group G, the FEV₁ was also significantly lower than the initial mean value in this group, whereas in group A this difference did not reach significance. However, the between-group differences for these values were not significant.

Table 1. Means of Pulmonary Function Tests and Gradients of Changes in Function in the Perioperative Period

Variable	Group	Predrug	Postdrug	End-test	Prepost gradient	Post-end gradient	Pre-end gradient	Quadratic effect
FVC	Atropine	2.35 ± 0.158	2.45 ± 0.157	2.20 ± 0.175	0.102 ± 0.032	-0.252 ± 0.060	-0.150 ± 0.059	-0.863 ± 0.217
	Glycopyrrolate	2.60 ± 0.163	2.65 ± 0.181	2.38 ± 0.165	0.054 ± 0.042	-0.273 ± 0.069	-0.220 ± 0.047	-0.595 ± 0.303
FEV ₁	Atropine	1.61 ± 0.126	1.77 ± 0.131	1.58 ± 0.131	0.156 ± 0.015	-0.192 ± 0.032	-0.036 ± 0.027	-1.124 ± 0.113
	Glycopyrrolate	1.92 ± 0.143	2.08 ± 0.167	1.85 ± 0.144	0.160 ± 0.045	-0.224 ± 0.042	-0.065 ± 0.024	-1.182 ± 0.307
(FEV ₁)/(FVC)	Atropine	0.68 ± 0.031	0.72 ± 0.031	0.72 ± 0.032	0.034 ± 0.009	0.001 ± 0.011	0.035 ± 0.014	-0.200 ± 0.059
	Glycopyrrolate	0.73 ± 0.024	0.78 ± 0.026	0.78 ± 0.023	0.046 ± 0.008	0.000 ± 0.016	0.046 ± 0.014	-0.273 ± 0.055
PFL	Atropine	4.37 ± 0.374	4.66 ± 0.355	3.97 ± 0.378	0.291 ± 0.091	-0.697 ± 0.155	-0.403 ± 0.173	-2.439 ± 0.578
	Glycopyrrolate	5.30 ± 0.398	5.79 ± 0.353	4.83 ± 0.372	0.496 ± 0.201	-0.961 ± 0.210	-0.466 ± 0.163	-3.934 ± 1.356

All values are mean ± SEM.

Abbreviations: FVC, forced vital capacity; FEV₁, forced expiratory volume in one second; PFL, peak expiratory flow.

The gradients between data points for all 4 responses (Figs. 1-3) and the quadratic effects do not differ significantly between group A and group G. There is thus no evidence of a difference in the pattern of response to atropine and glycopyrrolate.

Discussion

There are several reports detailing the deleterious effects of airway instrumentation on pulmonary mechanics and gas exchange, but all of these have been performed under local anesthesia (3,8-10,13). This study is the first to investigate changes in pulmonary mechanics in patients undergoing fiberoptic bronchoscopy under general anesthesia. It is also the first study to compare the effects of atropine and glycopyrrolate on pulmonary mechanics in patients with preexisting pulmonary disease.

Atropine, the traditional anticholinergic agent used in association with general anesthesia, became established in the first half of this century (14). The main purpose for its routine use was to reduce oral, pharyngeal, and bronchial secretions stimulated by the anesthetic agents in use at that time (15), and to prevent vagotonic effects on the heart, especially in response to anesthetic and surgical manipulations (16,17). Later it was used as an antimuscarinic agent to counteract the muscarinic effects of the use of cholinesterase inhibitors for the reversal of nondepolarizing muscle relaxants (18,7). The use of atropine for premedication has declined because of the introduction of less irritating inhalational anesthetics, although its undesirable side effects also contributed to its diminished routine administration (7). Atropine's side effects include tachycardia, occasionally fatal arrhythmias (2,19), dry mouth, central nervous symptoms (20), mydriasis, and paralysis of accommodation, as well as pyrexia (7,12). In addition, the duration of action of atropine is so shortlived (19,21) as to limit its uses perioperatively and as a bronchodilator (22).

The alternative anticholinergic drug, glycopyrrolate, has been in use since its introduction in 1962 for the control of gastric hyperacidity (23,24). Its advantages over atropine include a longer duration of action (7,25), less tachycardia (7,22,25-28), and greater antisialogogue effect (7,20,25,29-31). The quaternary ammonium structure of glycopyrrolate, as opposed to the tertiary ammonium form of atropine, reduces the penetration of the blood-brain barrier by glycopyrrolate (7,27,32,33). Central nervous system effects, which may be particularly hazardous in the elderly, are thus less likely with glycopyrrolate. Lastly, the disconcerting blurring of vision caused by atropine is reported not to occur with glycopyrrolate (31).

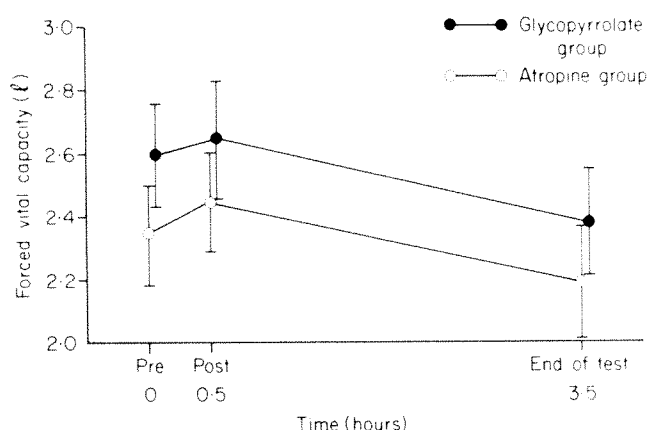


Figure 1. Forced vital capacity prior to any drugs (Pre), 30 min after administration of the anticholinergic drug (Post), and 2.5 hr after extubation (End of test). The mean for each value ± 1 SEM is shown.

Patients undergoing fiberoptic bronchoscopy for therapeutic or diagnostic procedures have a high incidence of poor pulmonary function, hypertension, and cardiac disease. In addition, many of the patients are elderly. Any decrease in pulmonary function is especially undesirable in any of these patients. Although atropine is relatively free of undesirable pulmonary side effects, the cardiovascular and central anticholinergic effects are particularly hazardous for many of these patients.

Gal and Suratt (28) reported that the vagal blockade with glycopyrrolate dilates large and small airways to the same extent as atropine, and that the effect is more sustained with the former drug. However, these studies were done in six healthy male volunteers, and patients with abnormal pulmonary function may not behave in the same manner as subjects with healthy lungs. Furthermore, their findings may not apply to patients undergoing endobronchial instrumentation.

The relevance of the findings of this study to other studies of patients undergoing similar procedures is confirmed by the remarkably similar age distribution between the patients in this study (52 ± 3.2 yr, range 24–66) and those reported in other series (52, range 18–72 yr, and 52, range 21–82 yr) (3,10).

Previous studies of fiberoptic bronchoscopy under local anesthesia with and without atropine premedication have shown that atropine effectively protected against the adverse effects of the procedure on pulmonary function (3,6,10), thus justifying the routine use of this drug prior to the procedure. Although our study showed improvement in pulmonary mechanics with both atropine and glycopyrrolate prior to instrumentation, neither anticholinergic drug provided complete protection against deteriorating lung

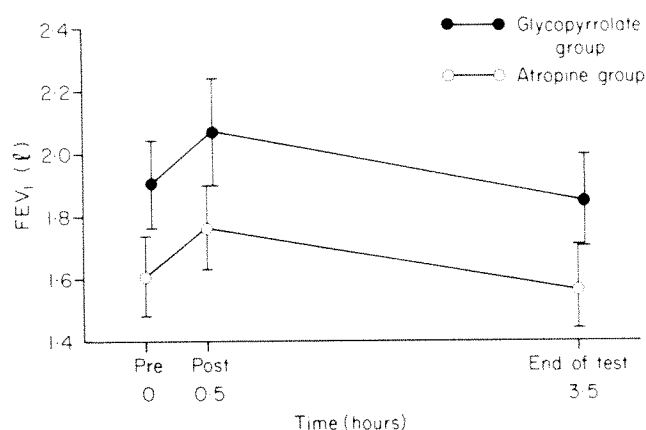


Figure 2. Forced expired volume in one second (FEV₁) prior to any drugs (Pre), 30 min after administration of the anticholinergic drug (Post), and 2.5 hr after extubation (End of test). The mean for each value ± 1 SEM is shown.

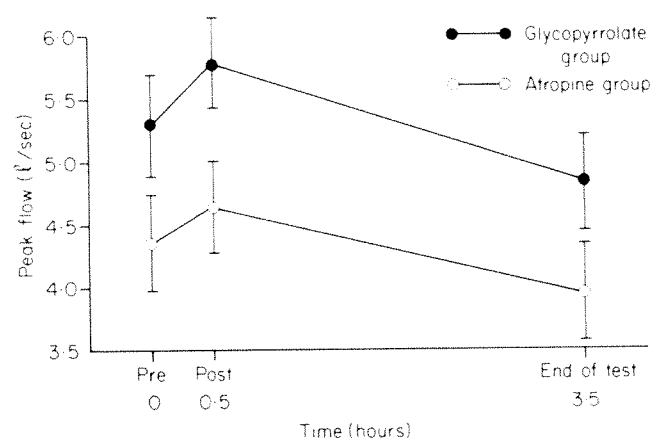


Figure 3. Peak expiratory flow (Peak flow) prior to any drugs (Pre), 30 min after administration of the anticholinergic drug (Post), and 2.5 hr after extubation (End of test). The mean for each value ± 1 SEM is shown.

mechanics after fiberoptic bronchoscopy under general anesthesia. We were unable to demonstrate any difference in the degree of protection afforded by either drug, and they may therefore be considered of equal value for this purpose.

The choice of anticholinergic agent can therefore be made on the basis of the actions of each drug on other systems. Thus, where the undesirable side effects of atropine, particularly those pertaining to the cardiovascular system, are likely to be harmful, glycopyrrolate may safely be substituted. As patients presenting for fiberoptic bronchoscopy are likely to have concomitant cardiovascular disease and are frequently elderly, glycopyrrolate would appear to be the anticholinergic agent of choice for this procedure.

The authors wish to thank Miss T. Webster and Mrs. E. Rosenheim for their technical assistance.

References

- Ikeda S, Yanai N, Ishikawa S. The flexible bronchofiberscope. *Keio J Med* 1968;17:1-16.
- Jones RE, Deutsch S, Turndorf H. Effects of atropine on cardiac rhythm on conscious and anesthetized man. *Anesthesiology* 1961;22:67-73.
- Neuhaus A, Markowitz D, Rotman HH, Wegg JG. The effects of fiberoptic bronchoscopy with and without atropine premedication on pulmonary functions in humans. *Ann Thorac Surg* 1978;25:393-8.
- Lindholm C, Ollman B, Schneider J et al. Flexible fiberoptic bronchoscopy in critical care medicine, diagnosis, therapy and complications. *Crit Care Med* 1974;2:250-9.
- Sackner MA, Wanner A, Landa J. Applications of bronchofiberscopy. *Chest* 1972;62(suppl)70S-8S.
- Belen J, Neuhaus A, Markovitz D, Rotman HH. Modification of the effect of fiberoptic bronchoscopy on pulmonary mechanics. *Chest* 1981;79:516-9.
- Ramamurthy S, Shaker MH, Winnie AP. Glycopyrrolate as a substitute for atropine in neostigmine reversal of muscle relaxant drugs. *Can Anaesth Soc J* 1972;19:399-411.
- Perreira W, Kovnat DN, Snider GL. A prospective cooperative study of complications following flexible fiberoptic bronchoscopy. *Chest* 1978;73:813-6.
- Salisbury BG, Metzger LF, Altose MD, Stanley NM, Cherniak NS. Effect of fiberoptic bronchoscopy on respiratory performance in patients with chronic airways obstruction. *Thorax* 1975;30:441-6.
- Zavala DC, Godsey K, Bedell GN. The response to atropine sulphate given by aerosol and intramuscular routes to patients undergoing fiberoptic bronchoscopy. *Chest* 1981;79:512-5.
- Mapleson WW. The elimination of rebreathing in various semi-closed anaesthetic systems. *Br J Anaesth* 1954;26:323-32.
- Bain JA, Spoerel WE. A streamlined anaesthetic system. *Can Anaesth Soc J* 1972;19:426-35.
- Albertini RE, Harrell JH, Moser KN. Management of arterial hypoxemia induced by fiberoptic bronchoscopy. *Chest* 1975;67:134-6.
- Weiner N. Atropine, scopolamine, and related antimuscarinic drugs. In: Gillman AG, Goodman LS, Rall TW, Murad F, eds. *The pharmacological basis of therapeutics*. 7th Ed. New York: Macmillan, 1985:130-44.
- Buxton DW. The use of scopolamine, morphine, atropine and similar drugs by hypodermic injection before inhalation anaesthesia. *Proc R Soc Med* 1911;4:43-56.
- Atkinson RS, Rushman GB, Lee JA. A synopsis of anaesthesia 8th ed. Bristol: John Wright & Sons, 1977:107.
- Stoelting RK. Psychological preparation and preoperative medication. In: Miller RD, ed. *Anesthesia*. New York: Church Livingstone, 1981:98.
- Wood M. Cholinergic and parasympathomimetic drugs. Cholinesterases and anticholinesterases. In: Wood M, Wood AJ eds. *Drugs and anesthesia*. Baltimore: Williams & Wilkin 1982:128.
- Eger EI II. Atropine, scopolamine and related compounds. *Anesthesiology* 1962;23:365-83.
- Mirakhor RK, Dundee JW, Clarke RSJ. Glycopyrrolate/neostigmine mixture for antagonism of neuromuscular block: comparison with atropine-neostigmine mixture. *Br J Anaesth* 1977;49:825-82.
- Wangerman RP, Hawk MH. The effects of neostigmine, atropine and scopolamine on human subjects. *Anesthesiology* 1942;3:24-36.
- Gal TJ, Suratt PM, Lu J-Y. Glycopyrrolate and atropine inhalation: comparative effects on normal airway function. *Am Rev Respir Dis* 1984;129:871-3.
- Sun DCH. Comparative study of the effect of glycopyrrolate and propantheline on basal gastric secretion. *Ann NY Acad Sci* 1962;99:153-7.
- Moeller HC. Physiological effects and clinical evaluation of glycopyrrolate in peptic ulcer disease. *Ann NY Acad Sci* 1962;99:158-62.
- Ostheimer GW. A comparison of glycopyrrolate and atropine during reversal of nondepolarizing neuromuscular block with neostigmine. *Anesth Analg* 1977;56:182-6.
- Klingenmaier CH, Bullard R, Thompson D, Watson R. Reversal of neuromuscular blockade with a mixture of neostigmine and glycopyrrolate. *Anesth Analg* 1972;51:468-72.
- Odoro KA. Glycopyrrolate methobromide. 2. Comparison with atropine sulphate in anaesthesia. *Can Anaesth Soc J* 1975;22:466-73.
- Gal TJ, Suratt PM. Atropine and glycopyrrolate effects on lung mechanics in normal man. *Anesth Analg* 1981;60:85-90.
- Wyant GM, Kao E. Glycopyrrolate methobromide. 1. Effect on salivary secretion. *Can Anaesth Soc J* 1974;21:230-41.
- Mirakhor RK, Dundee JW, Jones CJ. Evaluation of the anticholinergic actions of glycopyrronium bromide. *Br J Clin Pharmacol* 1978;5:77-84.
- Mirakhor RK, Dundee JW. Comparison of the effects of atropine and glycopyrrolate on various end-organs. *J Royal Soc Med* 1980;73:727-30.
- Prokakis AG, Harris GB. Comparative penetration of glycopyrrolate and atropine across the blood-brain and placental barriers in anesthetized dogs. *Anesthesiology* 1978;48:339-44.
- Paon WDM, Zaimis EJ. The methonium compounds. *Pharmacol Rev* 1952;4:219-53.

Epinephrine Reduces Systemic Absorption of Extradural Diacetylmorphine

M. A. Jamous, MD, C. W. Hand, BSc, GRSC, R. A. Moore, DPhil, FRSC,
P. J. Teddy, DPhil, FRCS, and H. J. McQuay, DM, FFARCS

JAMOUS MA, HAND CW, MOORE RA, TEDDY PJ, McQUAY HJ. Epinephrine reduces systemic absorption of extradural diacetylmorphine. *Anesth Analg* 1986;65:1290-4.

The effect of epinephrine on the vascular absorption of morphine from the extradural space is uncertain; this study examined the effect of epinephrine on the related but more lipophilic opiate diacetylmorphine (diamorphine, heroin) because any effects of vasoconstriction on diacetylmorphine absorption should be maximally apparent. With this experiment, we hoped to resolve whether epinephrine does or does not alter vascular absorption of extradurally injected opiates. Thirty patients undergoing lumbar laminectomy were given either extradural diacetylmorphine, 5 mg, extradural diacetylmorphine, 5 mg with 1:200,000 epinephrine, or 1:200,000 epinephrine followed 5 min later by 5 mg extradural diacetylmorphine. Plasma morphine concentrations were measured by radioimmunoassay because of the rapid conversion of diacetylmorphine to morphine in plasma; repeated blood samples were obtained the first 30 min after injection into the epidural space. Significantly lower plasma morphine levels occurred between 3 and 20 min when epinephrine was added to diacetylmorphine. Peak plasma mor-

phine levels (mean \pm SEM) were 179 ± 37 nmol/L with diacetylmorphine alone, 87 ± 16 nmol/L with diacetylmorphine and epinephrine given together and 44 ± 11 nmol/L with epinephrine pretreatment, all significantly different from one another. The mean peak plasma morphine concentration was 8.7 ± 1.1 min for diacetylmorphine alone, but addition of epinephrine (together or sequentially) meant that 15 of 20 patients had no peak level before 120 min. Epinephrine reduced absorption of diacetylmorphine from the extradural site by at least 55% over the first 30 min. The incidence of patients with more than 9 hr analgesic duration was significantly ($P = 0.033$) greater in patients who had diacetylmorphine and epinephrine. The use of diacetylmorphine as a model for lipophilic opiates showed that addition of epinephrine not only reduced systemic absorption but also increased analgesic duration. The addition of epinephrine to similarly lipophilic opiates should have the same clinically desirable consequence.

Key Words: ANALGESICS—diacetylmorphine (heroin). PAIN—postoperative. ANESTHETIC TECHNIQUES—epidural.

Drugs in the extradural space have three possible kinetic fates; they may be taken up into extradural fat, into the systemic circulation, or they may cross the dura mater and enter the spinal fluid and cord (1). Circumstances that reduce uptake of drug from the extradural space into the systemic circulation may enhance the specific spinal action of opiates by allowing more drug to diffuse across the dura mater (2,3). The addition of epinephrine should accomplish this end; vasoconstriction should severely restrict uptake of opiates into the blood, as it does for local anesthetics

(4). However, with regard to the most commonly used extradural opiate, morphine, there is little kinetic or clinical data to support this proposal. Some investigators have found epinephrine to have little effect on morphine uptake into blood (5,6), or into cerebrospinal fluid (6); by contrast, others have found delayed absorption and lower peak plasma morphine concentrations (7).

This study investigated the effect of epinephrine on the uptake of diacetylmorphine from the extradural space. Diacetylmorphine was chosen because it is structurally related to morphine but is much more lipophilic (8); any effects of vasoconstriction on its uptake should be maximally apparent. Diacetylmorphine has been given extradurally and produced excellent analgesia (9,10). Rapid early sampling points were planned to demonstrate fully any reduction of systemic absorption by epinephrine. The effects of

Received from the Department of Neurosurgery and the Nuffield Departments of Clinical Biochemistry and Anaesthetics, Radcliffe Infirmary, Oxford, England. Accepted for publication July 5, 1986.

Address correspondence to Dr. Moore, DPC/European Research Institute, Station Lane, Witney, Oxfordshire OX8 6AN.

pretreatment with epinephrine followed by diacetylmorphine administration were sought because epinephrine is known to take about 5 min to exert maximum vasoconstriction (11).

Methods

Thirty patients undergoing elective laminectomy for prolapsed lumbar intervertebral discs were studied; the design was open and sequential because the main object was to investigate plasma drug concentrations, and because there were no previous reports of the use of diacetylmorphine and epinephrine given together. Patients received general anesthesia, and at the end of surgery a catheter was placed into the lumbar extradural space under direct vision (9).

On return to the postoperative ward, patients were given an extradural dose of diacetylmorphine with or without epinephrine. The first ten patients (group 1) received 5 mg diacetylmorphine hydrochloride (Evans Medical, Beaconsfield, Bucks) diluted in 5 ml of water for injection. The next ten patients (group 2) were given 5 mg of diacetylmorphine hydrochloride diluted in 5 ml of a solution of 1:200,000 of epinephrine. The final ten patients (group 3) were first given a 2 ml injection of epinephrine 1:200,000 followed 5 min later by an injection of 5 mg diacetylmorphine hydrochloride in 5 ml water for injection; these patients thus had a lower total epinephrine dose, but a larger total extradural volume injected.

Venous blood samples (2 ml) were collected from a peripheral vein into tubes containing lithium heparin anticoagulant at 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 30, 60, and 120 min, timed from the end of the injection of diacetylmorphine. Samples were separated and plasma was stored frozen until analysis. Plasma morphine concentrations were measured because diacetylmorphine is rapidly deacetylated to monoacetylmorphine and morphine in plasma (12); morphine analysis was by radioimmunoassay (13).

The duration of analgesia was determined from the interval between the end of the diacetylmorphine injection and the time to the first subsequent analgesic dose. This interval, and any side effects, were recorded by the ward staff.

The maximum observed plasma morphine concentration (C_{peak}) and time of maximum concentration (T_{peak}) was noted for each patient; this was taken to be 120 minutes if no earlier maximum was seen. Areas under the plasma concentration-time curve for 0-30 min (AUC_{0-30}) and 0-120 (AUC_{0-120}) were calculated by the trapezoidal rule. Absorption rate constants (K_{abs}) were calculated for each patient using the following equation:

Table 1. Patient Demographics

	Group 1 ^a	Group 2 ^b	Group 3 ^c
Age	38.4 ± 3.1	38.7 ± 2.7	41.3 ± 1.8
Weight (kg)	70.6 ± 3.5	73.3 ± 3.1	76.2 ± 3.8
Sex (M/F)	4/6	6/4	8/2

All values are mean ± SE; there were no significant differences for age or weight.

^aExtradural diacetylmorphine hydrochloride (5 mg) diluted in 5 ml water for injection.

^bExtradural diacetylmorphine hydrochloride (5 mg) diluted in 5 ml of 1:200,000 epinephrine solution.

^cExtradural diacetylmorphine hydrochloride (5 mg) diluted in 5 ml water for injection preceded by 2 ml 1:200,000 epinephrine solution.

$$T_{peak} = -\frac{\log_e (k_{el}/k_{abs})}{(k_{abs} - k_{el})}$$

where T_{peak} was the time of peak plasma concentration, k_{abs} was the absorption half-life from the extradural space and k_{el} the elimination half-life of morphine in plasma. Diacetylmorphine is rapidly deacetylated to morphine in plasma (12) so, as previously (9), the elimination half-life for morphine was taken as 180 min.

Statistical analysis was with the Mann-Whitney U-test and Fisher's exact test; statistical significance was taken as $P < 0.05$. Mean values are given with the standard error of the mean.

Results

There were no significant differences between the three groups with regard to age or weight (Table 1). Patients experienced good pain relief. The only notable side effect was that three of the thirty patients required urinary bladder catheterization; there were no instances of itching or clinically apparent respiratory depression.

Plasma morphine concentrations were significantly lower between 3 and 20 min when diacetylmorphine was given with epinephrine (groups 2 and 3) than with diacetylmorphine alone (group 1; Table 2), but thereafter plasma morphine concentrations were not significantly different. In groups 2 and 3, whether epinephrine was administered before or together with the diacetylmorphine made no significant difference to the plasma morphine concentration at any time. However, mean plasma morphine concentrations were always lower after epinephrine pretreatment than after epinephrine coadministration.

The major effect of epinephrine on plasma morphine concentrations was in the first 30 minutes; there was a significant reduction in AUC_{0-30} for groups 2 and 3 compared with group 1. In the first 30 min the effect of epinephrine was to reduce diacetylmorphine

Table 2. Plasma Morphine Concentrations

Time (min)	Plasma morphine concentration (nmol/L)					
	Group 1	n	Group 2	n	Group 3	n
1	0.2 ± 0.2	9	3.1 ± 1.3	9	5.1 ± 1.1	10
2	20.9 ± 8.9	10	8.2 ± 4.9	8	7.3 ± 1.6	9
3	58.8 ± 1.4	10	11.8 ± 4.6 ^a	9	10.5 ± 2.5 ^b	10
4	88.3 ± 32.0	10	15.7 ± 5.5 ^b	9	15.5 ± 5.0 ^b	10
5	91.2 ± 28.5	10	32.1 ± 10.8 ^a	10	18.3 ± 5.9 ^b	10
6	134.0 ± 37.1	10	33.2 ± 11.7 ^b	10	23.4 ± 7.8 ^c	10
7	138.0 ± 42.3	10	37.4 ± 12.7 ^b	10	25.9 ± 8.2 ^c	10
8	120.7 ± 34.5	10	38.2 ± 12.0 ^b	10	27.4 ± 8.9 ^b	10
9	114.7 ± 32.4	9	39.9 ± 12.8 ^b	10	26.5 ± 8.2 ^c	10
10	156.4 ± 37.2	9	39.8 ± 13.0 ^c	10	27.9 ± 8.6 ^c	10
15	114.3 ± 21.7	10	46.3 ± 18.4 ^b	10	29.8 ± 9.2 ^c	10
20	84.4 ± 19.5	10	45.0 ± 15.3 ^a	10	25.5 ± 7.1 ^c	10
30	69.4 ± 17.6	10	52.8 ± 12.9	10	29.4 ± 8.3	10
60	79.9 ± 15.1	10	64.7 ± 11.9	10	34.6 ± 9.3 ^c	10
120	62.9 ± 11.2	10	74.9 ± 10.8	10	42.9 ± 10.6	10

All values are means ± SE.

^aSignificant difference from group 1, $P < 0.05$.^bSignificant difference from group 1, $P < 0.02$.^cSignificant difference from group 1, $P < 0.002$.

Table 3. Kinetic Parameters

	Group 1	Group 2	Group 3
AUC ₀₋₃₀ (min·nmol·L ⁻¹)	2799 ± 597	1186 ± 360 ^a	730 ± 212 ^a
AUC ₀₋₁₂₀ (min·nmol·L ⁻¹)	9260 ± 1705	7133 ± 1331	4016 ± 1062 ^a
C _{peak} (nmol/L)	179 ± 37	87 ± 16 ^b	44 ± 11 ^{c,d}
T _{peak} (min)	8.7 ± 1.1	—	—
Range	6-15	5-120 ^c	8-120 ^c
T _{1/2abs} (min)	1.24 ± 0.2	—	—

All values are mean ± SE for ten patients in each group. Values for T_{1/2abs} could not be calculated for groups 2 and 3. T_{peak} could not be measured for groups 2 and 3 because absorption was not complete by the last sampling point.

Abbreviations: AUC₀₋₃₀, area under the plasma concentration-time curve from 0 to 30 min; AUC₀₋₁₂₀, area under the concentration-time curve from 0 to 120 min; C_{peak}, peak plasma morphine concentration; T_{peak}, time of peak plasma morphine concentration; T_{1/2abs}, time of absorption half-life.

^aSignificant difference from group 1, $P < 0.02$.^bSignificant difference from group 1, $P < 0.05$.^cSignificant difference from group 1, $P < 0.002$.^dSignificant difference from group 2, $P < 0.02$.

removal into the systemic circulation by a mean of 55% in group 2 and 74% in group 3. This effect was not sustained, and only in group 3 where epinephrine pretreatment was used was AUC₀₋₁₂₀ reduced significantly (Table 3).

Peak plasma morphine concentrations were significantly higher with diacetylmorphine alone, and they occurred significantly earlier (Table 3). The mean time to reach a peak concentration was 8.7 min when diacetylmorphine was given alone, but it was very

much longer when epinephrine was administered also; seven of ten patients in group 2 and eight of ten in group 3 had not reached a peak plasma morphine concentration before the final 120 min sampling point.

With extradural diacetylmorphine alone, a mean absorption half-life of 1.24 min (range 0.76-2.4 min) could be calculated. For groups 2 and 3, in which epinephrine was given with the diacetylmorphine, absorption half-lives could not be calculated because of the long time to peak concentration (median 120 min or greater in each group). For both group 2 and group 3 the median absorption half-lives could not be calculated accurately, but were estimated to be in excess of 60 min, which was significantly longer than for diacetylmorphine alone ($P < 0.02$, Mann-Whitney U-test).

With extradural diacetylmorphine alone, the interval before additional analgesia was required averaged 7.3 ± 0.6 hr (range 3.8-11.0 hr). With coadministration of diacetylmorphine and epinephrine this interval increased to 12.2 ± 2.0 hr (range 6.0-24.1 hr), and with pretreatment with epinephrine the interval averaged 10.1 ± 1.8 hr (range 4.8-22.3 hr); these differences were not significant (Mann-Whitney U-test). Only one patient of the ten given diacetylmorphine alone had a duration of analgesia of more than 9 hr compared with ten of 20 patients given diacetylmorphine and epinephrine. Analyzed in this way, there was a significantly increased incidence of prolonged analgesic duration after administration of epinephrine with diacetylmorphine ($P = 0.033$, Fisher's exact test).

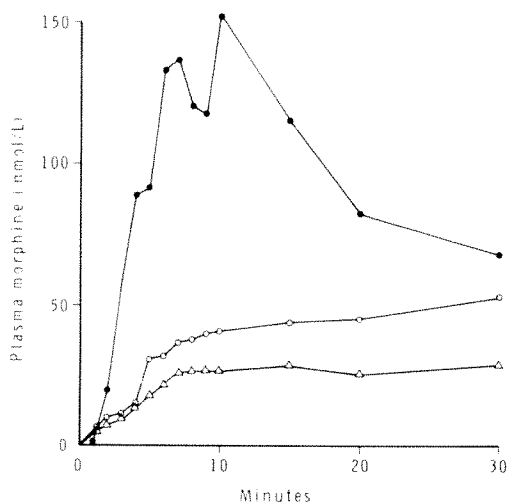


Figure 1. Mean plasma morphine concentrations after extradural injection of 5 mg diacetylmorphine. ●, group 1; ○, group 2; △, group 3.

Discussion

Vascular absorption of extradurally administered drugs is appreciable because the surface area of the extradural venous plexus is large. Vascular removal of local anesthetics from the extradural site can be reduced by agents that produce local vasoconstriction (1,7).

For extradural opiates, uptake of drug into the systemic circulation is similar to that after intramuscular administration (14), and will produce some supraspinal analgesia. However, to give selective spinal analgesia opiates must cross the dura mater (2,3). Reducing drug removal from the extradural space will increase the proportion of drug that crosses the dura mater, and should therefore enhance or prolong analgesia (15).

The results presented here indicate that epinephrine reduced significantly the rate of diacetylmorphine removal from the extradural space, presumably because of vasoconstriction. Over the first 30 min the magnitude of that reduction was some 55%, similar to the effect of epinephrine in slowing local anesthetic removal (4). The duration of the effect was only about 30 min, and thereafter plasma morphine concentrations were similar in all three patient groups.

However, there were several indications that group 3, where the epinephrine was given 5 min before diacetylmorphine, had particularly slow absorption. The peak concentration of plasma morphine was significantly lower by about 50% when epinephrine was administered before diacetylmorphine, as compared with coadministration. The AUC_{0-120} was significantly lower after epinephrine pretreatment compared with diacetylmorphine alone, in contrast to diacetylmorphine and epinephrine coadministration. In

addition, mean plasma morphine concentrations were always lower in group 3 than group 2. Because of the differences in the amounts of epinephrine used and total volumes of drug injected, it cannot be concluded that this form of administration would always be superior, but there are substantial indications that this may be so.

In the present study the analgesic measures did not support these kinetic data. Although an increased incidence of prolonged duration of analgesia was apparent in both groups given epinephrine, there was no difference between groups 2 and 3. Of course, the time to first analgesic demand is a crude analgesic measure; it is particularly inadequate to detect small differences when the sensitivity of the system is reduced by clustering at one end of the analgesic scale. Demonstration of significant analgesic differences between patients given extradural opiate with or after extradural epinephrine would require a much larger study with more precise analgesic measurements.

Can the results presented here for diacetylmorphine be extrapolated to the use of epinephrine with extradural morphine? Morphine has about 100 times lower lipophilicity than diacetylmorphine (8) and vascular absorption of extradural morphine may not be expected to be affected by vasoconstrictor additions. However, the time-course of appearance of morphine in the peripheral venous circulation is only slightly slower than diacetylmorphine (9,16) and is similar to that of local anesthetics whose absorption is delayed by epinephrine (4).

Reports of the kinetics of plasma morphine after coadministration of extradural morphine and epinephrine are confused. Although reduced peak plasma morphine values and delayed absorption after epinephrine have been reported in volunteers (7), other investigators found no kinetic differences after cesarian section (5). However, in the latter study, the time to peak plasma morphine concentration after extradural administration was about 21 min, which contrasts with other mean values of 7 min (9), 5–15 min (9,14,16), and 13 min (6,17). It may be, therefore, that absorption of drugs from the extradural space is altered during or soon after pregnancy (5).

None of these studies had many early sampling points. The unequivocal demonstration that epinephrine had significant effects on the vascular absorption of morphine from the extradural space would require multiple sample times soon after morphine administration, together with the best possible vasoconstriction. These conditions may be met by using a more concentrated epinephrine solution (1 in 100,000) to produce maximal vasoconstriction (1) before the extradural morphine is administered.

Such a study would have more than just academic significance; a positive result for both kinetics and analgesia would have important clinical implications for extradural morphine. The results from this study indicate that vasoconstricting agents could be used to prolong analgesia for the more lipophilic opiates.

We wish to thank Mr. C. B. T. Adams for allowing us to study his patients, the neurosurgery staff for their help, and the patients for their cooperation. CWH was supported by the Science and Engineering Research Council in cooperation with Reckitt & Colman Pharmaceutical, Hull, United Kingdom.

References

1. Bromage PR. Spinal epidural analgesia. Edinburgh: E & S Livingstone 1954.
2. Bullingham RES, McQuay HJ, Moore RA. Extradural and intrathecal narcotics. *Recent Advances in Anaesthesia and Analgesia* 1982;14:141-56.
3. Bullingham RES, McQuay HJ, Moore RA. Principles of use of extradural and intrathecal narcotics. In: Kauffmann L, ed. *Anaesthesia reviews 2*. Edinburgh: Churchill Livingstone 1983: 137-47.
4. Burfoot MF, Bromage PR. The effects of epinephrine on meperidine absorption from the spinal epidural space. *Anesthesiology* 1971;35:488-92.
5. Youngstrom PC, Cowan RI, Sutheimer C, Eastwood DW, Yu JCM. Pain relief and plasma concentrations from epidural and intramuscular morphine in postcesarian patients. *Anesthesiology* 1982;57:404-9.
6. Nordberg G. Pharmacokinetic aspects of spinal morphine analgesia. *Acta Anaesthesiol Scand* 1984;28:79 (Supp):6-38.
7. Bromage PR, Camporesi EM, Durant PA, Neilsen CH. Influence of epinephrine as an adjuvant to epidural morphine. *Anesthesiology* 1983;58:257-62.
8. Gibaldi M, Kanny JL. Drug absorption and the oral mucosa. *J Oral Ther Pharmacol* 1965;1:440-50.
9. Watson J, Moore A, McQuay H, Teddy P, Baldwin D, Allen M, Bullingham R. Plasma morphine concentrations and analgesic effects of lumbar extradural morphine and heroin. *Anesth Analg* 1984;63:629-34.
10. Teddy PJ, Adams CBT, Briggs M, Jamous MA, Kerr JH. Extradural diamorphine in the control of pain following lumbar laminectomy. *J Neurol Neurosurg Psych* 1981;44:1074-78.
11. The Pharmaceutical Codex. London: The Pharmaceutical Press, 1979.
12. Inturissi C, Umans J, Max M, Foley K, Schultz M, Shin S-U, Houde R. The pharmacokinetics of heroin in patients with chronic pain. *N Engl J Med* 1985;310:1213-7.
13. Moore RA, Baldwin D, Allen MC, Watson PJQ, Bullingham RES, McQuay HJ. Sensitive and specific morphine radioimmunoassay with iodine label: pharmacokinetics of morphine in man after intravenous administration. *Ann Clin Biochem* 1984;21:318-25.
14. Weddel SJ, Ritter RR. Serum levels following epidural administration of morphine and correlation with relief of postsurgical pain. *Anesthesiology* 1981;54:210-4.
15. Moore RA, Bullingham RES, McQuay HJ, Hand CW, Aspel JB, Allen MC, Thomas D. Dural permeability to narcotics: in vitro determination and application to extradural administration. *Br J Anaesth* 1982;54:1117-28.
16. Phillips DM, Moore RA, Bullingham RES, Allen MC, Baldwin D, Fisher A, Lloyd JW, McQuay HJ. Plasma morphine concentrations after thoracic extradural morphine or diamorphine. *Br J Anaesth* 1984;56:829-36.
17. Chauvin M, Samii K, Schermann JN, Sandouk P, Bourdon R, Viars P. Plasma pharmacokinetics of morphine after IM, extradural and intrathecal administration. *Br J Anaesth* 1982;54:843-7.

Note Added in Proof

A recent publication by Nordberg et al. (1986), in which four or five cerebrospinal fluid (CSF) and plasma samples were collected over 16-22 hr, demonstrates that peak plasma morphine concentrations were lower and CSF morphine concentrations higher after coadministration of extradural morphine and epinephrine than after morphine alone. (Nordberg G, Mellstand T, Borg L, Hedner T. Extradural morphine: influence of adrenaline admixture. *Br J Anaesth* 1986;58:598-604.) These differences were not statistically different; this underlines that rapid sampling of plasma, CSF, or both is required soon after extradural morphine and epinephrine administration to fully demonstrate the effects of extradural epinephrine on extradural morphine kinetics.

Priming with Atracurium: Improving Intubating Conditions with Additional Doses of Thiopental

Mohamed Naguib, MSc, FFARCSI, Mohamed Abdulatif, MSc, H. K. Gyasi, FFARCSI, and
G. H. Absood, PhD

NAGUIB M, ABDULATIF M, GYASI HK, ABSOOD GH.
Priming with atracurium: improving intubating conditions
with additional doses of thiopental. *Anesth Analg*
1986;65:1295-9.

The effects of different intubating doses of atracurium on the time of onset, and the effect of an additional dose of thiopental on intubating conditions, were studied in 72 patients divided into six groups (n = 12 in each). Stratified sampling was used to obtain an even sex distribution. Groups I, III, and V (controls) received atracurium as a single bolus dose of 0.4, 0.5 or 0.6 mg/kg respectively. Groups II, IV, and VI received an initial (priming) dose of 0.05 mg/kg followed 3 min later by 0.35, 0.45, or 0.55 mg/kg respectively. The time of onset, that is the time from the intubating dose to complete suppression of the train-of-four (TOF) response, was significantly accelerated after administration of

atracurium in divided doses. Increasing the intubating dose of atracurium after an initial 0.05 mg/kg from 0.35 to 0.55 mg/kg did not result in further significant acceleration of the onset time, but resulted in prolongation of the duration of neuromuscular blockade. When divided doses of atracurium were given, administration of 2 mg/kg thiopental (in addition to the 5 mg/kg used for induction) before the injection of the intubating dose resulted in improvement of intubating conditions as reflected by statistically significant changes in intubating scores. This result was probably due to the increase by thiopental in the depth of anesthesia. Therefore, when thiopental is given as supplement, the priming technique can be made to provide better conditions for tracheal intubation in less than 90 sec.

Key Words: INTUBATION—endotracheal. NEUROMUSCULAR RELAXANTS—atracurium.

Acceleration of the onset of nondepolarizing muscle relaxants would be advantageous in situations where rapid tracheal intubation is required and succinylcholine is undesirable or contraindicated. Such acceleration has been achieved by using the "priming principle" (1-6), which refers to the administration of a small (priming) dose of a nondepolarizing muscle relaxant a few minutes before the administration of the larger (intubating) dose (7).

Miller (7) has pointed out that to optimize the outcome of this maneuver, the priming dose, the intubating dose, and the time interval between these two doses must be closely defined. Using atracurium, we recently reported that the optimal priming dose appeared to be 0.05 mg/kg and the optimal priming interval was 3 min (5,6). However, acceleration of neu-

romuscular blockade with a priming dose is not consistently associated with the best intubating conditions in all patients (4-6).

This study was undertaken to evaluate the effect of different intubating doses of atracurium on the time of onset of muscle paralysis and the contribution of the size of the intubating dose and of an incremental dose of thiopental (in addition to the dose used for induction) on the intubating conditions in patients receiving atracurium in divided doses.

Methods

After institutional approval, 72 ASA physical status I or II patients undergoing elective surgical procedures were studied. All patients were free from neuromuscular, renal, or hepatic disease and were not taking any drugs known to interfere with neuromuscular function. Informed consent was obtained. All patients were premedicated with 10-15 mg diazepam orally 90 min preoperatively.

An intravenous infusion of lactated Ringer's solution with 5% dextrose was established before in-

Received from the Department of Anesthesiology and the Biostatistics Unit, Department of Community Medicine, King Faisal University, Al Khobar, Saudi Arabia. Accepted for publication July 17, 1986.

Address correspondence to Dr. Naguib, Department of Anesthesiology, King Faisal University, King Fahd Hospital, PO Box 2208, Al Khobar 31952, Saudi Arabia.

Table 1. Grading of Intubating Condition^a

Score	Intubating conditions
0	Cords abducted, good visualization, no patient movement
1	Cords abducted, good visualization, diaphragmatic movement with intubation
2	Cords slightly adducted, fair visualization, coughing with intubation
3	Cords adducted, difficult visualization, gross body movements, and coughing with intubation

^aFrom Fahey et al. (9).

duction. The ECG and nasopharyngeal temperature were monitored continuously by a Medishield M1 monitor. Blood pressure was measured every 5 min by an electronic oscillotonometer (Dinamap).

In all patients, anesthesia was induced with fentanyl, 2 μ g/kg, and thiopental, 5 mg/kg and was maintained with 70% nitrous oxide in oxygen.

After induction of anesthesia, the thumb of a restrained arm was attached to a force displacement transducer to record the response of the adductor pollicis to supramaximal stimulation of the ulnar nerve at the elbow using a Myotest peripheral nerve stimulator (Biometer) and a neuromuscular function analyzer with a continuous pen and paper recorder (Myograph 2000, Biometer) (8). The preload tension on the thumb was maintained at 300 g throughout the investigation.

Four square wave impulses of 0.2 msec duration and 2 Hz frequency were repeated every 10 sec. Once a steady state twitch was established, patients were assigned randomly to one of six groups ($n = 12$ in each). Stratified sampling was used to obtain an even sex distribution. Groups I, III, and V (controls) received atracurium as a single bolus dose of 0.4, 0.5, or 0.6 mg/kg, respectively. Groups II, IV, and VI received an initial dose of 0.05 mg/kg followed 3 min later by 0.35, 0.45, or 0.55 mg/kg, respectively.

The train-of-four (TOF) ratio (the amplitude of the fourth evoked response as a fraction of the first evoked response: T_4/T_1) was recorded before the administration of atracurium in all groups. The maximum effect of the priming dose on the TOF ratio was also recorded.

Groups II, IV, and VI were subdivided into equal subgroups, a and b ($n = 6$ in each). Groups IIb, IVb, and VIb received an additional dose of 2 mg/kg thiopental just before the injection of the intubating dose of atracurium, whereas groups IIa, IVa, and VIa did not receive additional thiopental.

Onset time (time from the end of injection of the intubating dose to the development of complete

Table 2. Demographic Data

Group ^a	Age (Yr)	Body weight (kg)
I	29.2 \pm 7.8	65.8 \pm 10.6
II	30.2 \pm 8.3	61.4 \pm 10.5
III	32.2 \pm 8.1	65 \pm 11.8
IV	31 \pm 6.1	63.6 \pm 8.1
V	31.5 \pm 9.6	65.4 \pm 8.6
VI	33.1 \pm 7.8	64.1 \pm 8.3

^aFor each group, $n = 12$, M/F = 6/6.

suppression of all four responses to TOF stimulation) was determined. Tracheal intubation was performed by a single observer who was "blind" to the patient groups immediately after complete TOF suppression in all groups. Intubating conditions (Table 1) were scored as described by Fahey et al. (9). Ventilation was controlled to maintain normocapnia and end-tidal CO_2 was monitored by Datex infrared CO_2 analyzer. Times from the injection of the intubating dose of atracurium to 10% and 20% recovery of the first twitch (T_1) of TOF were recorded.

Statistics

Two independent-sample Student's *t*-tests were employed to test the differences in the mean onset times and recovery times between the control and divided dose groups at each dose.

To estimate, simultaneously, the effects of the size of the intubating dose and the method of administration on the various parameters observed in all the groups, factorial experiment (10) was applied. In the factorial experiment the first factor was the dose and had three levels, and the second factor was the technique of administration of atracurium and had two levels. Analysis of variance was performed to test the significance for each factor and for the interaction between factors.

The Wilcoxon test was applied to compare the effects of the priming doses on the TOF ratios. Intubating scores were compared using the Kruskal-Wallis test. The values were considered to be statistically significant when $P < 0.05$.

Results

Results are expressed as means \pm SD. All groups were comparable with respect to age and weight (Table 2). The mean TOF ratio decreased to 0.9 ($P < 0.05$) after the priming dose. The mean onset times in groups II, IV, and VI that received atracurium in divided doses

Table 3. Priming Dose, Priming Interval, Intubating Dose, Onset Time, and Recovery of Twitch Height to 10% and 20%

Groups	Priming dose (mg/kg)	Priming interval (min)	Intubating dose (mg/kg)	Onset Time ^a (sec)	10% recovery of T ₁ (min)	20% recovery of T ₁ (min)
I	—	—	0.4	123.3 ± 36.8	32 ± 4.2	34.5 ± 4.3
II	0.05	3	0.35	85 ± 43 ^b	31.5 ± 3.9	34.2 ± 4.3
III	—	—	0.5	119.5 ± 25.8	34.4 ± 3.9	36.8 ± 9.3
IV	0.05	3	0.45	71.1 ± 14.1 ^b	37.3 ± 7	41 ± 7.6
V	—	—	0.6	95.4 ± 38.4	45 ± 8.3 ^c	49.2 ± 8.5 ^c
VI	0.05	3	0.55	68.7 ± 20.4 ^b	45 ± 3.8 ^c	47.8 ± 4.4 ^c

^aOnset time is the time from the intubating dose of atracurium to complete suppression of train-of-four.^bThe onset times were significantly ($P < 0.05$) faster in groups who received atracurium in divided dose.^cTimes to 10% and 20% recovery of T₁ were significantly prolonged in groups V and VI.

(Table 3) were, respectively, 85 ± 43 , 71.1 ± 14.1 , and 68.7 ± 20.4 sec. These times were significantly shorter than for groups I, III, and V (123.3 ± 36.8 , 119.5 ± 25.8 , and 95.4 ± 38.4 sec, respectively) who were given the same amounts of atracurium but in a single injection. Increasing the size of the intubating doses in groups II, IV, and VI did not result in any further significant acceleration in onset time. Analysis of variance did not yield any significant interaction between the different total doses and the method of administration of atracurium that might affect onset time. In patients who had no priming dose, increasing the intubating dose of atracurium from 0.4 mg/kg to 0.6 mg/kg did not result in a significant acceleration in the onset time.

The duration of neuromuscular blockade as assessed by times to 10% and 20% recovery of T₁ was not significantly affected by the method of administration of atracurium (Table 3). Recovery was significantly delayed in group V and VI who received a total dose of 0.6 mg/kg atracurium when compared to other groups who received either 0.4 or 0.5 mg/kg total dose. No interaction was found between the different doses and the method of administration of atracurium that might affect the duration of neuromuscular blockade.

There were no significant differences in the intubating scores in patients who received atracurium without an additional dose of thiopental, either in a single dose or in divided doses, and intubating conditions were satisfactory (intubating scores of 2 or less). The size of the intubating dose had no influence on intubating conditions. However, additional thiopental given before administration of the intubating doses in group IIb, IVb, and VIb significantly improved intubating conditions as measured by intubating scores. Excellent intubating conditions (score of zero) were obtained in 5 patients in groups IIb and IVb and in 4 patients in group VIb. In contrast only one patient in groups IIa, IVa, and VIa had excellent intubating conditions (Table 4).

Table 4. Intubating Conditions

Group	n	Intubating conditions			
		0	1	2	3
I	12	2	5	5	0
IIa	6	1	3	2	0
IIb ^a	6	5	1	0	0
III	12	3	5	4	0
IVa	6	1	2	3	0
IVb ^a	6	5	1	0	0
V	12	3	4	5	0
VIa	6	1	3	2	0
VIb ^a	6	4	2	0	0

^aThere was significant improvement in the intubating conditions ($P < 0.05$) in patients who received increments of thiopental before the administration of the intubating doses of atracurium.

Discussion

Use of succinylcholine to provide rapid and ideal intubating conditions has been customary, despite its many potential side effects (11), because of the lack of a better alternative. Most studies indicate that tracheal intubation cannot be accomplished in less than 2 min after the administration of large doses of nondepolarizing muscle relaxants (7). However, it has been demonstrated that the onset of action of nondepolarizing relaxants can be accelerated by the use of a priming dose (1-6). Because of the large margin of safety of neuromuscular transmission, 70% of the receptors can be blocked with no interference in the response to a single impulse (12). Small doses of nondepolarizing muscle relaxants are expected to occupy some of the receptors without blocking neuromuscular transmission, but subsequent doses will have a more rapid and profound effect (7).

In this study, administration of atracurium in divided doses resulted in a significant acceleration in the onset time, permitting tracheal intubation within 90 sec or less (Table 3). After the priming dose of 0.05 mg/kg given 3 min before the intubating dose, increasing the intubating dose of atracurium from 0.35 to 0.55 mg/kg did not accelerate onset of neuromus-

cular paralysis significantly but prolonged the duration of action with each increase in dose. This result may indicate that the time necessary for agonist-receptor interaction cannot be reduced with the dose range employed in this study.

Using divided doses of vecuronium, Schwarz et al. (2) attempted intubation when the twitch tension decreased to 15–20% of control. They found that three of eight patients who received 0.015 mg/kg vecuronium and two of 12 patients who received 0.02 mg/kg had only good, not excellent intubating conditions, with diaphragmatic movement on intubation. Miller (7) noted that studies of intubating conditions are notoriously difficult to interpret, and suggested that tracheal intubation should be attempted only after complete disappearance of twitch tension. However, waiting until complete suppression of twitch tension after administration of atracurium in divided doses does not provide uniformly excellent intubating conditions (5,6). Depth of anesthesia is one of the factors contributing to the adequacy of the intubating conditions. In contrast to other studies (1–4), patients in our studies were premedicated with oral diazepam only and had minimal doses of drugs used during induction of anesthesia, in an attempt to simulate the emergency situation.

For good intubating conditions, the cough reflex must be suppressed. Nondepolarizing muscle relaxants have different effects on different muscle groups. The diaphragm is less susceptible to the effects of neuromuscular relaxants than are other muscles (13,14). Recently, a more than twofold difference between the diaphragm and the adductor pollicis with respect to their sensitivity to pancuronium has been shown in humans (15). This finding is further evidence that depression of thumb responses to nerve stimulation does not equate with diaphragmatic paralysis; perhaps the onset of diaphragmatic paralysis yields a better correlation with intubating conditions.

Relaxation of the jaw and vocal cords are other factors indicating the adequacy of intubating conditions. It would be ideal to have a precise method for measurement of the relaxation of jaw and vocal cords. Thiopental by itself in a dose of 5 mg/kg has been reported to relax the jaw sufficiently to permit laryngoscopy (16). However, thiopental in doses used clinically is known not to have any direct effect on neuromuscular transmission (17). However, deepening the level of anesthesia by increments of thiopental just before the administration of an intubating dose of nondepolarizing muscle relaxant significantly improved the intubating conditions, as observed in this study. Therefore, it appears that administration

of thiopental before intubating doses can produce better intubating conditions with priming doses of atracurium.

In conclusion, this study demonstrates that the administration of atracurium in divided doses results in a significant acceleration of the onset of neuromuscular block. Increasing the size of the intubating dose from 0.35 to 0.55 mg/kg atracurium after priming with 0.05 mg/kg did not affect the onset time significantly but resulted in prolongation of the duration of action with the higher doses used. Intubating conditions were not related to the onset of neuromuscular block or the size of the intubating dose. In patients who received divided doses of atracurium the improvement of intubating conditions was maximal only when supplemental thiopental (2 mg/kg) was administered before the injection of the intubating dose. In this way the priming technique can be made to provide even better intubating conditions in less than 90 sec.

We wish to express our gratitude to Professor Richard Bodman for his support and advice, and to Mrs. Merlinda B. Francisco for typing this manuscript.

References

1. Gergis SD, Sokoll MD, Metha M, Kemmotsu O, Rudd GD. Intubation conditions after atracurium and suxamethonium. *Br J Anaesth* 1983;55(Suppl 1):83S–6S.
2. Schwarz S, Ilias W, Lackner F, Mayrhofer O, Foldes FF. Rapid tracheal intubation with vecuronium. The priming principle. *Anesthesiology* 1985;62:389–91.
3. Metha MP, Choi W, Gergis SD, Sokoll MD, Adolphson A. Facilitation of rapid sequence endotracheal intubations with divided doses of non-depolarizing neuromuscular blocking drugs. *Anesthesiology* 1985;62:392–5.
4. Doherty WG, Breen PJ, Donati F, Bevan RD. Accelerated onset of pancuronium with divided doses. *Can Anaesth Soc J* 1985;32:1–4.
5. Naguib M, Gyasi HK, Abdullatif M, Absood GH. Rapid tracheal intubation with atracurium. A comparison of priming intervals. *Can Anaesth Soc J* 1986;33:150–6.
6. Naguib M, Abdullatif M, Absood GH. The optimal priming dose for atracurium. *Can Anaesth Soc J* 1986;33:453–7.
7. Miller RD (Editorial). The priming principle. *Anesthesiology* 1985;54:381–2.
8. Viby-Mogensen J. Clinical evaluation of neuromuscular transmission. *Br J Anaesth* 1982;54:209–23.
9. Fahey MR, Morris RB, Miller RD, John YJ, Cronelly R, Gen-carelli P. Clinical pharmacology of ORG NC 45 (Norcuron): a new non-depolarizing muscle relaxant. *Anesthesiology* 1981;55:6–11.
10. Daniel WW, ed. *Biostatistics foundation for analysis in the*

- health sciences. 3rd ed. John Wiley & Sons. New York, 1983:238-47.
11. Durant NN, Katz RL. Suxamethonium. *Br J Anaesth* 1982;54:195-208.
 12. Paton WDM, Waud DR. The margin of safety of neuromuscular transmission. *J Physiol (London)* 1967;191:59-90.
 13. Foldes FF, Monte AP, Brunn HM, Wolfson B. Studies with muscle relaxants in unanesthetized subjects. *Anesthesiology* 1961;22:230-6.
 14. Tran DQ, Amaki Y, Ohta Y, Nagashima H, Duncalf D, Foldes FF. Simultaneous in vivo measurement of NM block on three muscles. *Anesthesiology* 1982;57:A276.
 15. Donati F, Antzaka C, Bevan DR. The diaphragm and adductor pollicis dose-response curves for pancuronium. *Anesthesiology* 1985;63:A322.
 16. Young HSA, Clarke RSJ, Dundee JW. Intubating condition with AH 8165 and suxamethonium. *Anaesthesia* 1975;30:30-3.
 17. Lee-Son S, Waud BE, Waud DR. A comparison of the potency of a series of barbiturates at the neuromuscular junction and on the central nervous system. *J Pharmacol Exp Ther* 1975;195:251-6.

Acetaldehyde Syndrome after Celiac Plexus Alcohol Block

Junko Noda, MD, Shinichiro Umeda, MD, Kenjiro Mori, MD, Tatsushige Fukunaga, MD, and Yasuhiko Mizoi, MD

NODA J, UMEDA S, MORI K, FUKUNAGA T, MIZOI Y. Acetaldehyde syndrome after celiac plexus alcohol block. *Anesth Analg* 1986;65:1300-2.

In the course of celiac plexus alcohol block, facial flushing, palpitations, and hypotension are occasionally incurred in some patients. We hypothesized that the phenomenon represents acetaldehyde syndrome, not response to increased blood levels of ethanol as might be supposed. In order to prove our hypothesis, we selected five patients scheduled to undergo celiac plexus alcohol block, and, with their consent, we measured blood concentration of ethanol and acetaldehyde before and for 6 hr after the block. We also determined

the phenotypes of aldehyde dehydrogenase (ALDH) in their hair roots. We found that "flushers" are found exclusively among subjects without ALDH I, and that their blood levels of acetaldehyde were significantly higher than those of "non-flushers" within 10 min after the block. The flushers also gave histories of facial flushing after ingestion of small amounts of ethanol. On the basis of such histories one can anticipate whether acetaldehyde syndrome is likely or unlikely to accompany the block.

Key Words: ALCOHOL—nerve blocks. METABOLISM—acetaldehyde syndrome.

Although major complications are infrequent during blocks of the celiac plexus with alcohol, patients occasionally experience facial flushing, palpitation, and diaphoresis after the injection of ethanol. We hypothesized that individual differences in the metabolism of ethanol might be responsible for these reactions. The investigation was designed to test this hypothesis.

Materials and Methods

We studied five patients who were scheduled to undergo celiac plexus alcohol block to relieve abdominal cancer pain. Each gave consent to the study. Celiac plexus block was performed in each with 15 ml of 99.5% ethanol according to the technique described by Moore (1). Venous blood was taken from subjects immediately before and after the procedure, with five more samples taken at 1-hr intervals.

Determination of Blood Ethanol and Acetaldehyde

One milliliter of heparinized venous blood was immediately added to 6 ml of ice-cold 0.6N perchloric

acid in saline. The precipitated proteins were separated out by centrifugation at 4000 rpm. Two milliliters of the supernatant were aspirated and put into a vial, sealed with a Teflon-coated rubber stopper, and incubated for 30 min at 65°C in the sampling turntable; the gas in the vial above the liquid phase was automatically taken by means of the electro-pneumatic dosing system and analyzed with a Perkin-Elmer F-45 Head Space Analyzer with FID detector. Head space conditions and acetaldehyde calculations have been previously described (2). The amount of acetaldehyde formed by the addition of perchloric acid to a 10 mM solution of ethanol was about 1 μ M (3).

Estimation of the Phenotypes of Aldehyde Dehydrogenase

About 20 hair roots from the head were obtained from each subject. Two kinds of aldehyde dehydrogenase (ALDH) phenotypes in the hair roots were determined by isoelectric focusing using the method of Goedde et al. (4).

Results

The five subjects fell into two groups according to their ALDH phenotype. One ($n = 3$) had the usual ALDH phenotype, with both ALDH I and II isozymes having low and high K_m for acetaldehyde, respec-

Received from the Department of Anesthesiology, Faculty of Medicine, Kyoto University, and the Department of Legal Medicine, Faculty of Medicine, Kobe University, Kobe, Japan. Accepted for publication July 15, 1986.

Address correspondence to Dr. Noda, Department of Anesthesiology, Faculty of Medicine, Kyoto University, Shogoin kawaharacho 54, Sakyo-ku, Kyoto, 606, Japan.

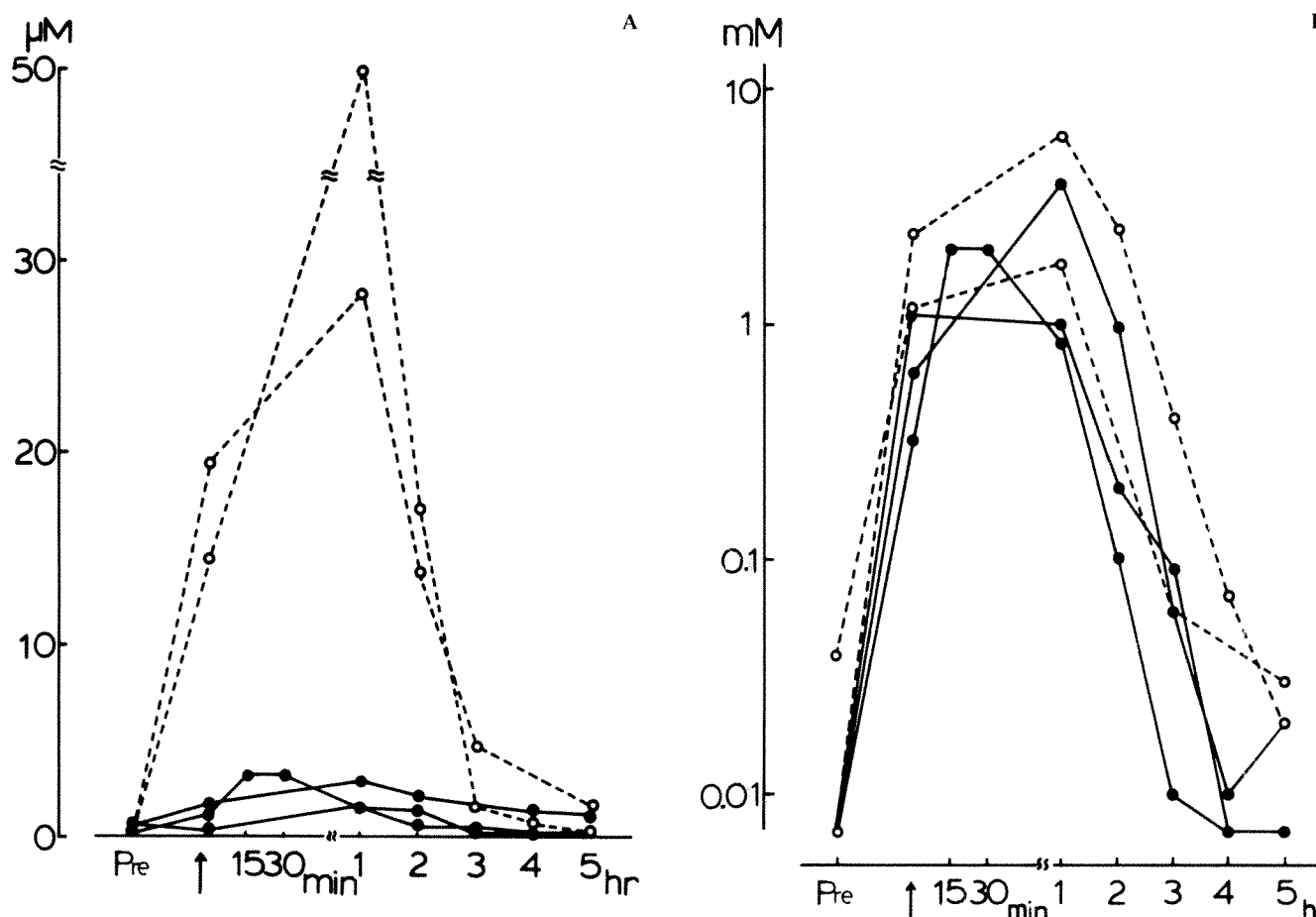


Figure 1. Blood concentration of acetaldehyde (A) and ethanol (B) in 5 subjects. Usual ALDH group (●—●); atypical ALDH group (○---○). Injection time is indicated by the arrow at time zero.

tively. The other group ($n = 2$) had an unusual ALDH phenotype that was deficient in ALDH I isozyme.

Before the block, physical findings and laboratory data were not significantly different between the two groups, except that the two subjects with the unusual ALDH phenotype gave a history of untoward reactions to alcohol ingestion. After the block, both subjects with unusual ALDH experienced facial flushing, palpitations, and general fatigue within 30 min. In one of them transient hypotension and respiratory distress were also observed, as was severe erythema, the latter gradually subsiding over 6 hr. The three subjects with the usual ALDH phenotype showed none of those symptoms.

The blood concentrations of acetaldehyde and ethanol are shown in Figures 1A and B. Acetaldehyde concentrations are significantly different in the two groups. In the two subjects with the unusual ALDH, the blood acetaldehyde level increased immediately after the block, the maximum level ranging from 28.31 to 49.36 μM . In the subjects with the usual ALDH

phenotype, peak acetaldehyde level ranged from 1.72 to 3.30 μM . Blood levels of ethanol were similar in the two groups of patients.

Discussion

Celiac plexus alcohol block is a safe, effective method for relief of pain due to inoperable abdominal carcinoma, especially carcinoma of the pancreas. After completion of the block, however, some patients experience facial flushing, palpitations, and other reactions even though they have shown no such symptoms in previous test blocks with local anesthetics. It has hitherto been believed that these symptoms represent acute alcohol intoxication. However, our survey of the literature revealed no report of the possible relation of these symptoms to an acetaldehyde syndrome produced by celiac plexus alcohol block. The connection occurred to us during previous experiments with acetaldehyde syndrome after alcohol ingestion (5).

Acetaldehyde syndrome, resulting from accumulation of acetaldehyde in the blood, is clinically diagnosed by facial and bodily flushing, palpitations, and hypotension. However, diagnosis depends upon measurement of blood acetaldehyde levels (6).

In our present study, measurements of blood acetaldehyde concentrations were made in five subjects before and after celiac plexus blocks. The results confirmed our hypothesis. Blood levels of acetaldehyde in the "flushers" were about 20 times higher than maximum concentrations seen in "nonflushers." The ALDH phenotype based on study of hair roots identified the flushers as ALDH I-deficient, and the nonflushers as subjects with the usual ALDH phenotype. The results are in accordance with our previous experiments on alcohol ingestion (5). We estimate from our previous autopsy data that about 38% of the Japanese are ALDH I-deficient (7). The frequency of facial flushing after the alcohol block agrees with this percentage.

In our subjects, blood alcohol levels showed no significant difference between flushers and nonflushers. The levels we saw were almost identical with those reported by Thompson et al. (8), and were much lower than the level taken as the legal definition of alcohol intoxication. It is, therefore, unlikely that acute alcohol intoxication is caused by celiac plexus block with 15 ml of 99.5% ethanol.

Our ALDH I-deficient patients also gave a history of facial flushing after ingestion of small amounts of alcohol. Knowledge of patients' susceptibility to liquor is important in identifying patients likely to develop this acetaldehyde syndrome after alcohol block

of the celiac plexus. Patients may have alcohol injections other than those made to block the celiac plexus. The alcohol injections that are made for relief of pain may involve injection of alcohol into the subarachnoid space. However, the volume of alcohol used for intrathecal injection is so small that it appears unlikely that this syndrome would develop after intrathecal injections of alcohol.

References

1. Moore DC. Regional block: intercostal nerve block combined with celiac plexus (splanchnic) block. 4th ed. Springfield: Charles C Thomas, 1981:145-62.
2. Eriksson CJP, Sippel HW, Forsander OA. The determination of acetaldehyde in biological samples by head-space gas chromatography. *Anal Biochem* 1977;80:116-24.
3. Eriksson CJP, Mizoi Y, Fukunaga T. The determination of acetaldehyde in human blood by the perchloric acid precipitation method: the characterization and elimination of artefactual acetaldehyde formation. *Anal Biochem* 1982;125:259-63.
4. Goedde HW, Agarwall DP, Harada S. Genetic studies on alcohol-metabolizing enzymes: detection of isozymes in human hair roots. *Enzyme* 1980;25:281-6.
5. Mizoi Y, Tatsuno Y, Adachi J et al. Alcohol sensitivity related to polymorphism of alcohol-metabolizing enzymes in the Japanese. *Pharmacol Biochem Behav* 1983;18:127-33.
6. Ritchie JM. The aliphatic alcohols. In: Gilman AG, Goodman LS, Gillman A, eds. *The pharmacological basis of therapeutics*, 6th ed. New York: Macmillan Publishing, 1980:377-90.
7. Kogame M, Mizoi Y. The polymorphism of alcohol and aldehyde dehydrogenase in the Japanese and its significance in ethanol metabolism. *Jpn J Alcohol and Drug Dependence* 1985;20:122-42.
8. Thompson GE, Moore DC, Bridenbaugh LD, Artin RY. Abdominal pain and alcohol celiac plexus nerve block. *Anesth Analg* 1977;56:1-5.

Evaluation of the Toxicity of Subarachnoid Clonidine, Guanfacine, and a Substance P-Antagonist on Rat Spinal Cord and Nerve Roots:

Light and Electron Microscopic Observations after Chronic Intrathecal Administration

Torsten Gordh Jr, MD, Claes Post, PhD, and Yngve Olsson, MD PhD

GORDH T Jr, POST C, OLSSON Y. Evaluation of the toxicity of subarachnoid clonidine, guanfacine, and a substance P-antagonist. Light and electron microscopic observations after chronic intrathecal administration. *Anesth Analg* 1986;65:1303-11.

Clonidine has been reported to produce analgesia in man after epidural and intrathecal administration. In the present investigation the α_2 -adrenoceptor agonists clonidine and guanfacine were tested to evaluate their potential spinal neurotoxic effects. Rats were injected daily for 14 consecutive days via catheters implanted in the intrathecal space. Clonidine was administered at a dose of 1.63 μ g or 16.3 μ g, and guanfacine at 16.3 or 75 μ g. After perfusion with a buffered 3% glutaraldehyde solution, the spinal cords and nerve roots were taken for neuropathological analysis using light and electron microscopy. Compared to animals injected

with 0.9% saline, clonidine and guanfacine gave rise to no detectable neurotoxic changes in the doses employed. An additional group of rats had intrathecal injections of a substance P-antagonist (D-Arg¹, D-Trp^{7,9}, Leu¹¹)-substance P (spantide) with known neurotoxic effect as a test of the histotechnical methods used. Degenerative lesions, with a preference for the ventral horns, were consistently present in the grey matter of the cord in these animals. We conclude that the absence of detectable changes in rats given clonidine and guanfacine is probably a real expression of the low degree of toxicity for these compounds on rat spinal cord and nerve roots and not an artifact of the sensitivity of the histotechniques applied. The doses of clonidine administered were considerably greater than those reported to produce clinical analgesia.

Key Words: SYMPATHETIC NERVOUS SYSTEM, α -ADRENOCEPTOR AGONISTS—clonidine, guanfacine.

Advances in the understanding of the physiology and pharmacology of pain and its modulation have resulted in a number of substances with great potential value in the treatment of clinical pain. Examples of such compounds are agonists to α_2 -, serotonin, and adenosine receptors, as well as physostigmine and somatostatin (1-6). Systemic and subarachnoid administration of α_2 -adrenoceptor agonists in animals produces a powerful, long-lasting antinociceptive effect, antagonized by specific α_2 -adrenoceptor antag-

onists but not by naloxone (1). This response indicates a mode of action different from that of opioids and represents a novel principle in the treatment of pain. Clonidine, an α_2 -adrenoceptor agonist, has been reported to potentiate spinal morphine analgesia and to delay the development of tolerance to morphine if the two drugs are administered together (2). There are several clinical reports indicating an analgesic effect of clonidine after oral, intravenous, epidural, and intrathecal administration (7-10). Epidural or subarachnoid use of the α_2 -adrenoceptor agonist guanfacine has not been reported in man but in animals subarachnoid guanfacine produces analgesia of longer duration than clonidine (Post, unpublished results). The mechanism for production of analgesia by epidurally or subarachnoidally administered α_2 -adrenoceptor agonists is believed to be activation of α_2 -adrenoceptors (11) located postsynaptically (12) in the dorsal horn of the spinal cord (13), resulting in de

This work was supported by grants from the Bank of Sweden Trecentenary Foundation (81/120, A. Tamsen) and from the Swedish Medical Research Council, project 12X-03020.

Received from the Department of Anaesthesiology and the Laboratory of Neuropathology, Institute of Pathology, Uppsala University, Uppsala; and ASTRA Research and Development Laboratories, Södertälje, Sweden. Accepted for publication July 21, 1986.

Address correspondence to Dr. Gordh, Department of Anaesthesiology, University Hospital, S-751 85 Uppsala, Sweden.

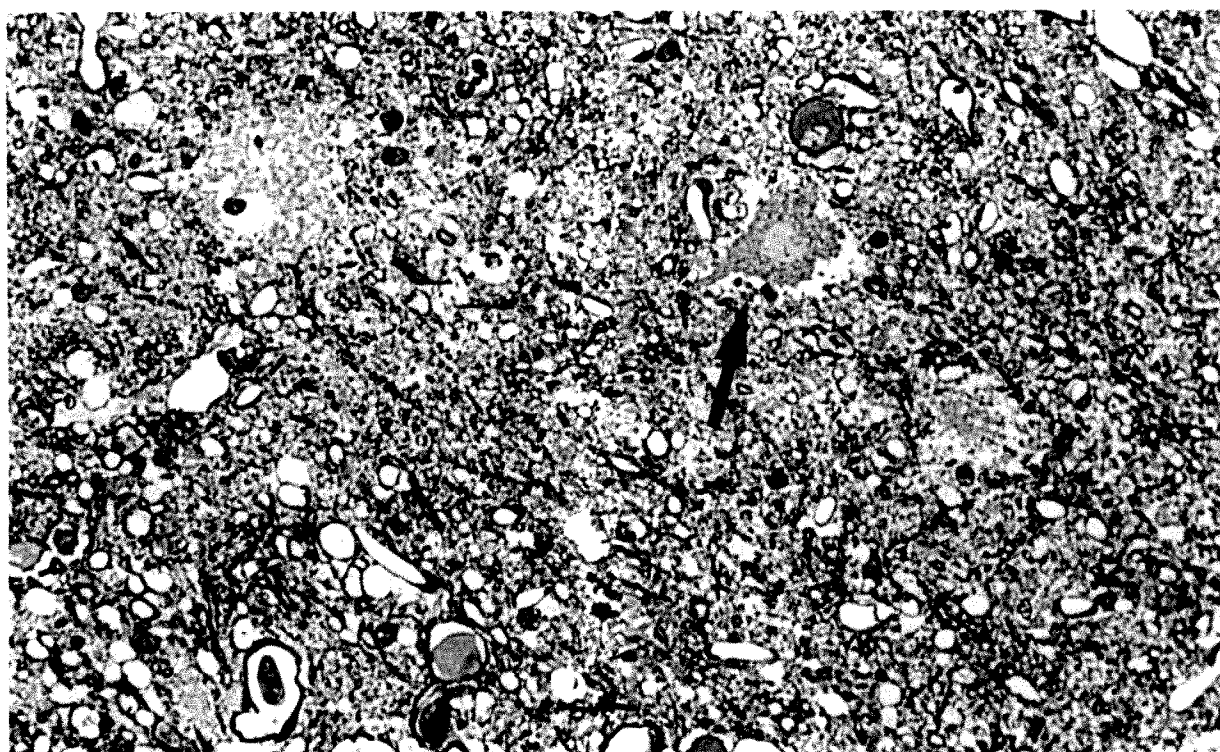


Figure 1. Ventral horn of lumbar spinal cord from spantide-treated rat. Note extensive necrosis of the neuronal bodies (arrow) and spongy appearance indicating edema. Toluidine blue stain.

creased transmission of nociceptive signals. Supraspinal actions of these drugs probably add to their analgesic effects (14).

There are thus reasons to believe that spinal α_2 -adrenoceptor agonists might be useful in the treatment of severe pain. Before introducing such compounds into clinical use, potential adverse effects should be carefully studied. The present investigation is one in a series of experiments designed to analyze the possibilities and limitations of α_2 -adrenoceptor agonists in the treatment of severe pain (15-18). In this study, using a rat model, daily intrathecal injections of clonidine and guanfacine were given under controlled circumstances and possible spinal neurotoxicity investigated by light and electron microscopy.

Materials and Methods

Surgical Procedure

Male Sprague-Dawley rats (ALAB, Sollentuna, Sweden) weighing 320-340 g were used. The drugs were administered through indwelling catheters, with the tip in the lumbar intrathecal space (19). The animals were anesthetized with an aqueous solution contain-

ing 42.5 g/L chloral hydrate, 90 g/L ethanol, 428 ml/L propylene glycol, 9.75 g/L pentobarbital, and 21 g/L magnesium sulphate. The catheter used was PE10, stretched to approximately half the original diameter when immersed in water of 75°C. Neurological complications caused by the otherwise too stiff catheter were thus minimized. An incision was made through the atlantooccipital membrane. The catheter was inserted approximately 8.5 cm, which left the tip of the catheter in the intrathecal space at the level of L1-2. To ascertain correct placement of the catheters, on the day after the operation 0.75 mg of lidocaine (50 mg/ml, ASTRA Läkemedel AB, Södertälje, Sweden) was injected, followed by 10 μ l of 0.9% saline to flush the catheter. All animals developing a bilateral motor blockade in the hind legs within 30 sec were included in the study. After operation and testing with lidocaine, the rats recovered in the animal rooms for 5-7 days.

Drugs and Injection Protocol

The animals meeting the criteria for inclusion in the study were randomly assigned to one of eight groups: 1) clonidine 1.63 μ g ($n = 6$); 2) clonidine 16.3 μ g ($n = 6$); 3) guanfacine 16.3 μ g ($n = 6$); 4) guanfacine 75 μ g ($n = 6$); 5) saline (vehicle) ($n = 6$); 6) cannulated animals in which no drug was injected ($n = 6$); 7) an

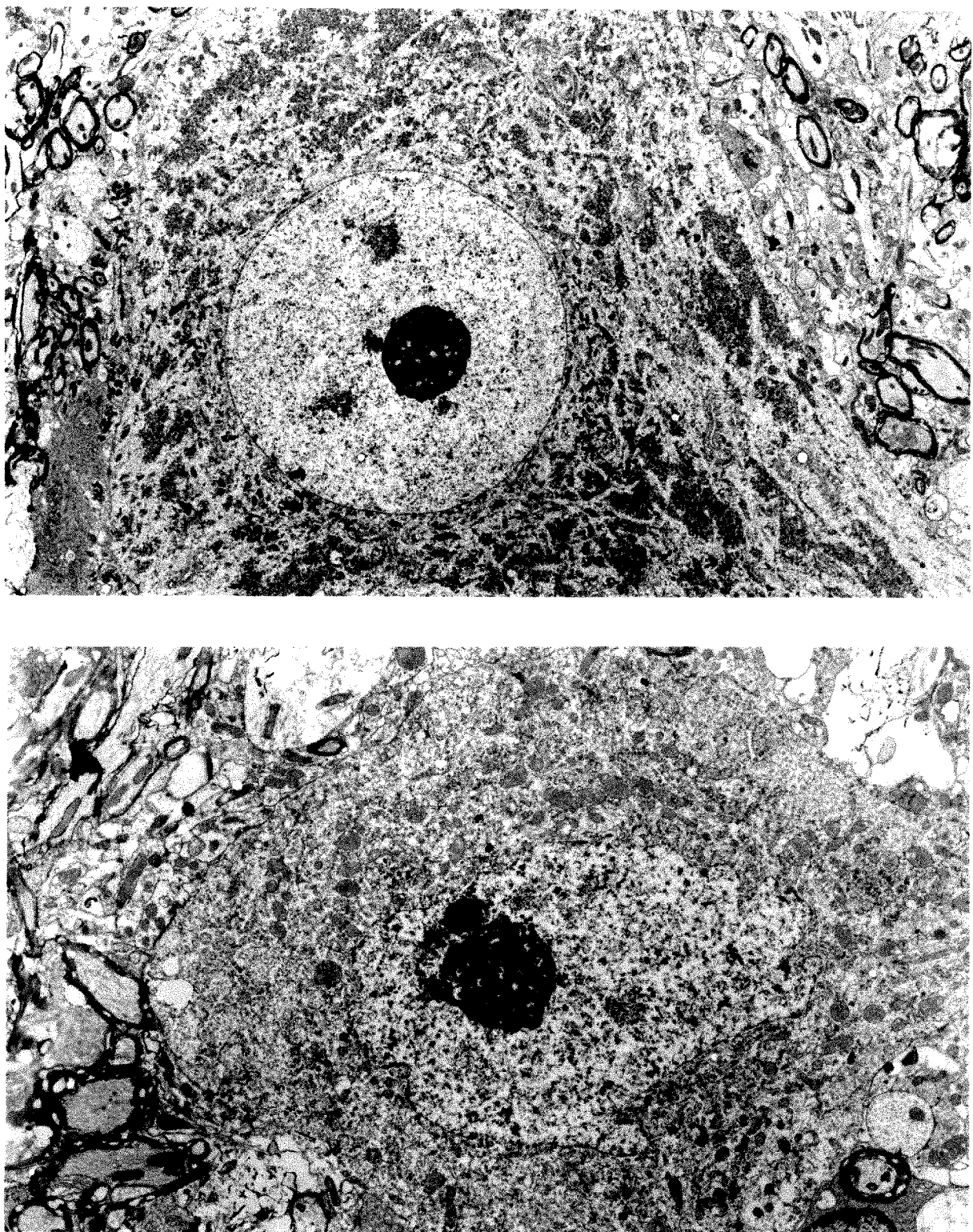


Figure 2. (A) Lumbar spinal cord from spantide-treated rat of apparently normal behavior. Ventral motor neuron appears normal. (Electron microscopy, $\times 1200$). (B) Ventral motor neuron from the same animal and spinal level shown in (A). Note irregular shape of the cell and nuclear membranes (Electron microscopy, $\times 2800$).

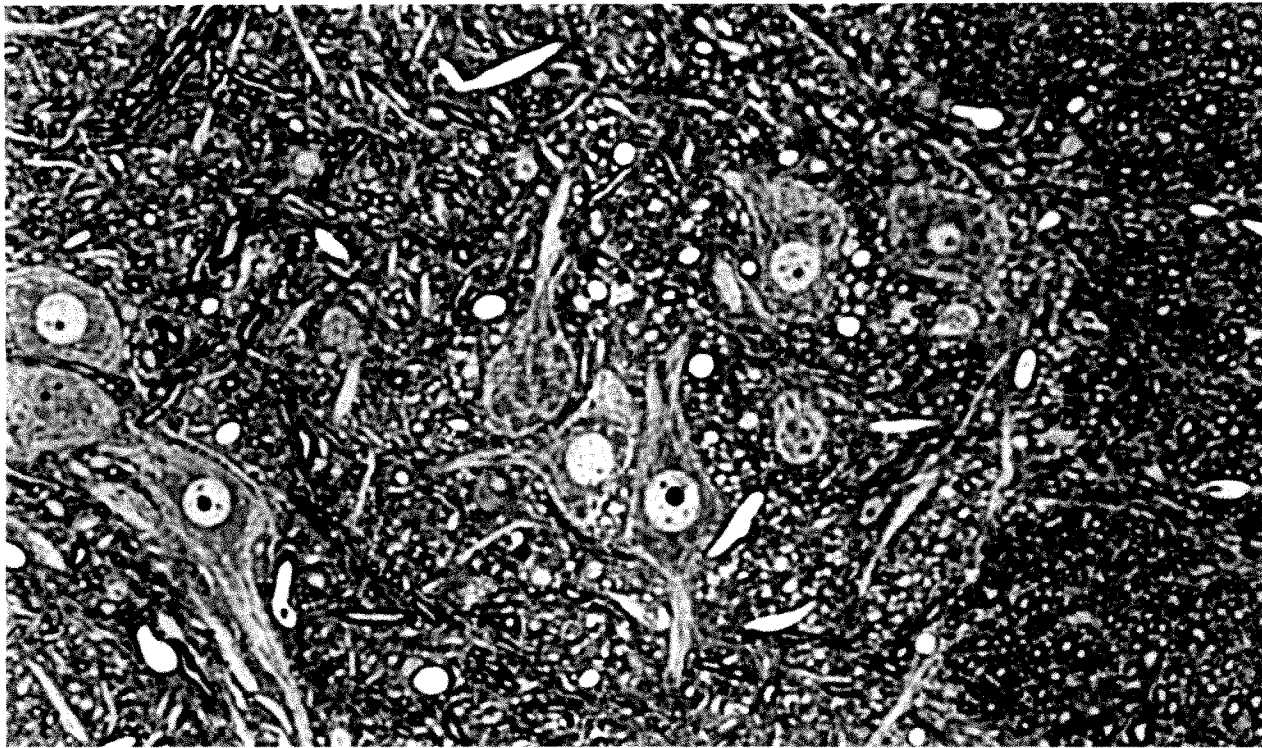


Figure 3. Lumbar spinal cord from rat treated with 16.3 μ g clonidine for 14 consecutive days. Figure shows ventral horn with motor neurons of normal appearance. Toluidine blue stain.

age-matched group of animals not operated upon ($n = 3$); 8) and animals given a substance P-antagonist, (D-Arg¹, D-Trp⁷⁻⁹, Leu¹¹)-substance P (spantide) (Peninsula Lab, Belmont, CA), in a dose of 2 μ g ($n = 3$). Clonidine (Boehringer-Ingelheim) and guanfacine (Sandoz) were given intrathecally in a volume of 15 μ l, and the catheter was flushed with 10 μ l of 0.9% saline. In the saline group, the animals were given 25 μ l of 0.9% saline. Injections were made in each animal once daily between 9:00 and 10:00 AM for 14 days.

The dose levels of clonidine and guanfacine were chosen on the basis of their antinociceptive effects in rats (Post, unpublished results). Clonidine doses of approximately 1–3 μ g/kg have previously been reported to produce analgesia with tolerable side effects in humans after epidural administration (9). Spantide, injected as a single dose only, was included as a test of our histotechnical methods. This substance causes neuronal damage in the grey matter of the spinal cord (20). These animals were killed 24 hr after the injection.

Tissue Preparation

On the day of the last injection, the animals were anesthetized with sodium pentobarbital, 60 mg/kg intraperitoneally. Heparin, 20 IU, was administered intravenously to prevent intravascular coagulation. When an animal was nonresponsive to tail pinching, the chest was opened. The right atrium was opened to permit exsanguination, after which a blunt 19-gauge stainless steel cannula was inserted into the ascending aorta via the left ventricle and sutured in this position.

The fixative procedure for light and electron microscopy was performed by perfusing the animals with 200 ml of 0.9% saline at room temperature, in order to clear the vascular system of blood. Saline perfusion was followed, without interruption of the stream, by perfusion with 250 ml of 3% glutaraldehyde in 0.1 M phosphate buffer with an osmolality of 290 mosm/kg, adjusted to pH 7.4 at room temperature. The perfusion fluids were delivered by a peristaltic pump delivering a pulsative flow of 50 ml/min, which was estimated to be approximately equal to the reported cardiac output of the rat (21).

In addition, 0.5 ml of glutaraldehyde solution was injected through the intrathecal catheter. The spinal column was dissected and the spinal cord was exposed by laminectomy. The cord was carefully excised and immersed in a glutaraldehyde solution of the same

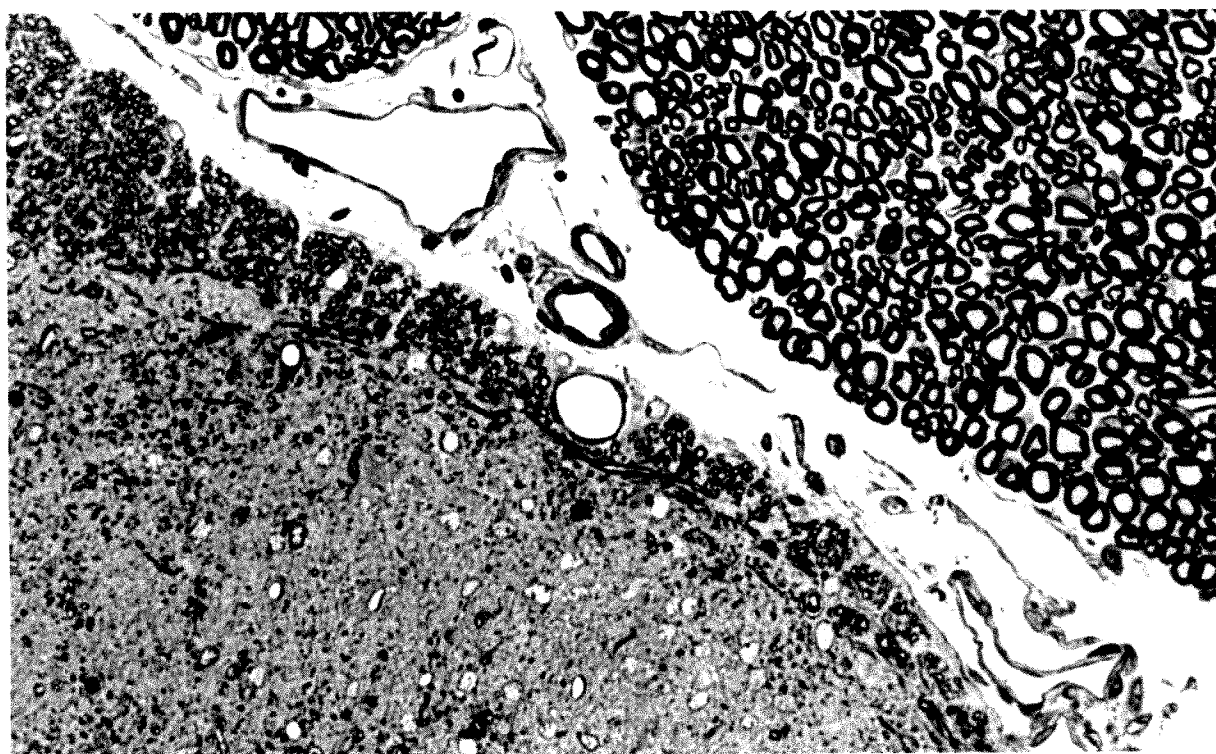


Figure 4. Dorsal horn and intradural part of dorsal root have a normal appearance in rat treated with 16.3 μ g clonidine for 14 days. Toluidine blue stain.

composition as that used for the perfusion fixation. The tissues were then stored at 4°C in this solution until further processing. Samples were taken from the cervical, thoracic, and lumbar segments of each spinal cord, including the intradural parts of the spinal nerve roots. For light microscopy the spinal cord tissue samples were embedded in paraffin, sectioned and stained with hematoxylin and eosin and luxol fast blue.

Corresponding samples were postfixed in 1% osmium tetroxide, rinsed in 0.15 M sodium-cacodylate buffer, contrasted with 1% uranylacetate in 50% ethanol and dehydrated in a graded series of ethanol. This was followed by infiltration with propylene oxide and epoxy after which the sections were embedded in epoxy resin (Agar 100 Resin[®], Agar Aids, Essex, England). One micron thick sections were cut from the entire cross area of the cord and stained with toluidine blue. They were used for light microscopy and for selection of areas for electron microscopy.

For electron microscopy the dorsal roots and dorsal horns from cervical, thoracic, and lumbar parts of the spinal cord from each animal were selected. Sections of 30 nm were viewed in a Philips electron microscope (EM 201, Philips, Eindhoven, The Netherlands), with lead citrate used for contrast. The light and electron microscopy were performed with coded sections by

a microscopist unaware of which treatment the animal had received.

Results

None of the control rats or the rats given clonidine or guanfacine showed evidence of neurological impairment when examined in their cages during the course of the 14 day trial. The fixative procedure for microscopy functioned well. There was uniform toluidine blue staining of structural details in the epoxy sections and there were no erythrocytes present in the capillaries.

Changes Caused by the Experimental Procedure in Control Rats

A mild compression of the cord was usually found in the operated rats along the course of the catheter. In a few cases the degree of deformation was marked. In all catheterized animals a mild increase in the num-

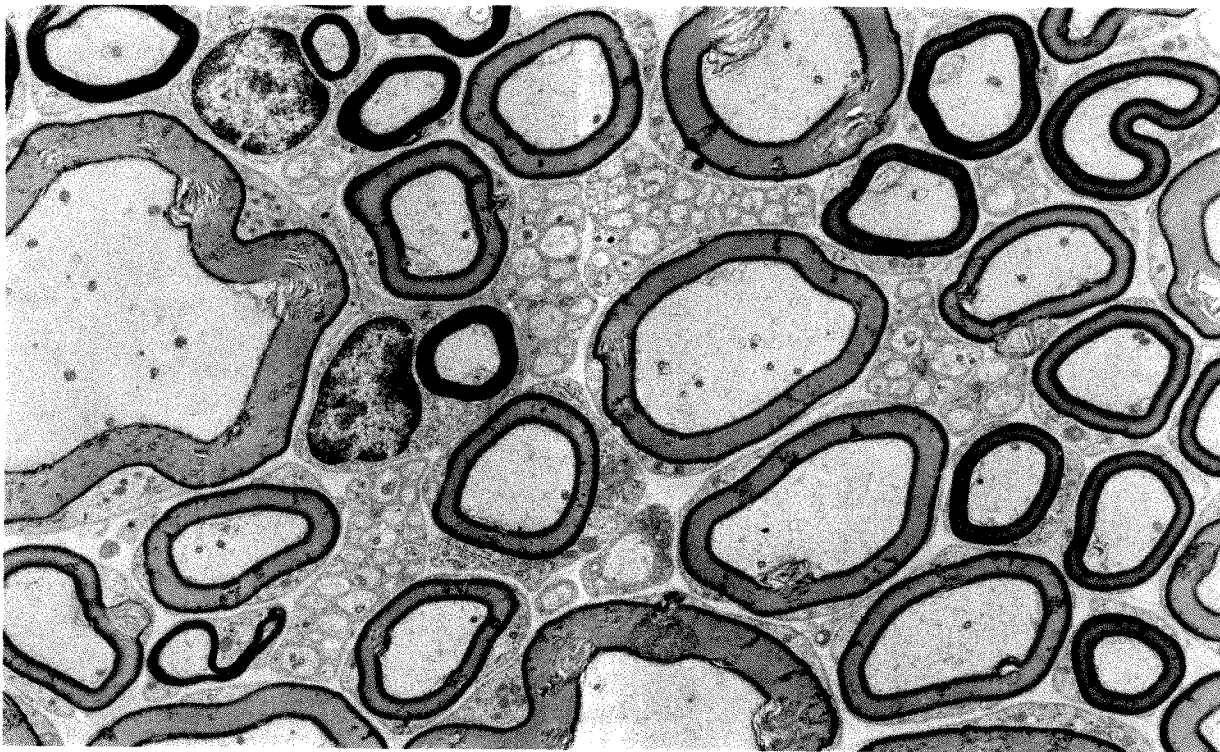


Figure 5. Intradural part of dorsal root of clonidine-treated rat (16.3 μ g). Note normal appearance of axons and myelin. In a few large fibers, splitting is seen in the myelin sheets. This is a preparation artifact also present in control animals (Electron microscopy, $\times 2800$).

ber of mononuclear inflammatory cells was evident close to the catheter and adjacent leptomeninges. The catheters were surrounded by a narrow zone of reactive tissue changes. The inflammatory reaction was less pronounced in the rats in whom an intrathecal catheter had been inserted but injections had not been given. In unoperated rats no cellular or tissue reaction was present.

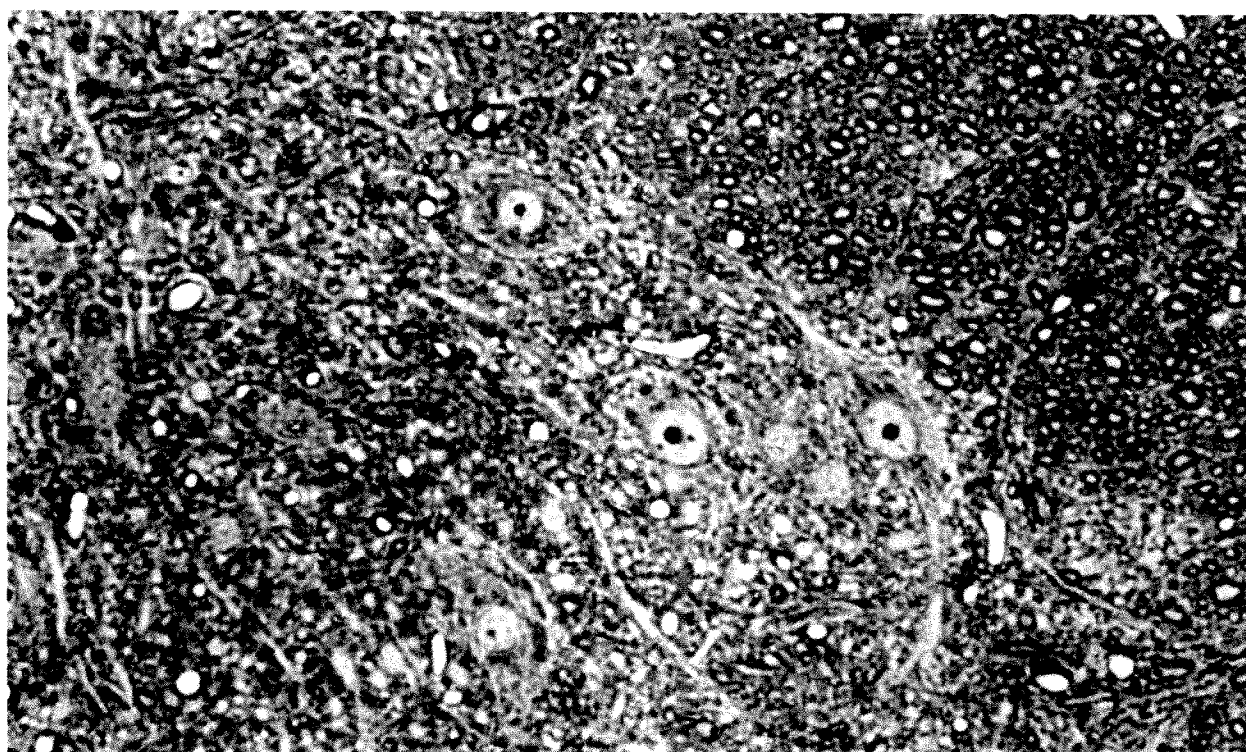
The ventral motor neurons and the neurons in the dorsal horn appeared normal. The intradural parts of the roots were normal as well. The long spinal tracts showed no signs of injury and spongiose appearance of the myelin sheets was not seen under light microscopy. There was no myelin damage, which would have appeared as asymmetry in the myelin pattern. Electron microscopically the dorsal nerve roots were well-preserved as shown by absence of splitting of the myelin sheet. In the larger myelin sheets, however, a concentric split of the myelin was commonly seen, a well-known phenomenon in tissue handled for electron microscopy. The mitochondria, microtubules, and neurofilaments of the axons and Schwann's cells were normal.

Spantide-Treated Rats

Some of the spantide-treated rats had paralysis of the hind legs. Light microscopy showed extensive necrosis of the neuronal bodies in both the ventral and dorsal horns in one animal (Fig. 1). The lesions were less pronounced in the dorsal horn. The lesions extended for some sections both rostrally and caudally from the tip of the catheter. Pycnotic cell nuclei were seen. In another rat, of apparently normal behavior, the lesions were less pronounced, and normal motor neurons could be seen adjacent to neurons in which changes in the shape of the cell membrane and nucleus were evident (Fig. 2A,B). The axons in the long tracts of the cord and the nerve roots were not affected. The intraparenchymatous blood vessels appeared normal. Sections taken from cord levels further from the tip of the catheter were entirely normal. Electron microscopy revealed different degrees of karyolysis, severe dendritic edema, and infiltration of inflammatory cells in the grey matter.

Clonidine-Treated Rats

Microscopic examination of the spinal cords from rats given clonidine for 14 days showed no changes apart from the mild deformation caused by the catheter, similar to that observed in control animals. The local tissue reaction in the leptomeninges and the super-



ficial parts of the cord was of the same character and magnitude as in the control rats that received vehicle. The long tracts of the cord showed no evidence of atrophy or loss of myelin. Glial cell proliferation, as judged by the number and position of glial cell nuclei, was not seen. The vessels were similar to those seen in control rats. The grey matter of the cord did not show any changes. The cell bodies of the neurons had normal shapes and the typical central position of the nuclei with prominent nucleoli (Fig. 3). There were no changes in appearance of the Nissl bodies.

Particular emphasis was directed to the light and electron microscopic appearance of the nerve roots and the dorsal horn. By light microscopy no differences could be detected between the animals injected with clonidine and control animals (Fig. 4). Electron microscopically, the dorsal nerve roots did not differ from the control animals (Fig. 5). No differences were present between the two clonidine groups or between the clonidine groups and the control groups. No signs of diffuse neuronal damage, or damage to certain cell types, indicative of a general toxic effect of clonidine was observed either by light or electron microscopy. The histological picture of neuronal structures close to the distal end of the catheter, where the concentrations of the test drug were the highest did not differ from more remote areas in the same animal.

Figure 6. Lumbar spinal cord from rat treated with guanfacine, 1 μ g, during 14 consecutive days. Motor neurons and myelin appear normal. Toluidine blue stain.

Guanfacine-Treated Rats

At light microscopic level no differences were detected, compared to the control groups. There were no differences in the appearance of the cord between the animals given low or high doses of guanfacine. The long spinal tracts and nerve roots were normal as was the grey matter of the cord. In comparison with the control groups, no differences were seen in the dorsal horns. Generally, the histological picture was uniform in the guanfacine groups, the clonidine groups, and the control groups (Figs. 6,7). Electron microscopically there were no differences from the control groups in the dorsal nerve roots.

Discussion

Potential spinal neurotoxicity should be investigated in animals before clinical experiments are started using spinal administration of new drugs. Remarkably many agents have been used by clinical investigators without such preliminary screening. When spinal

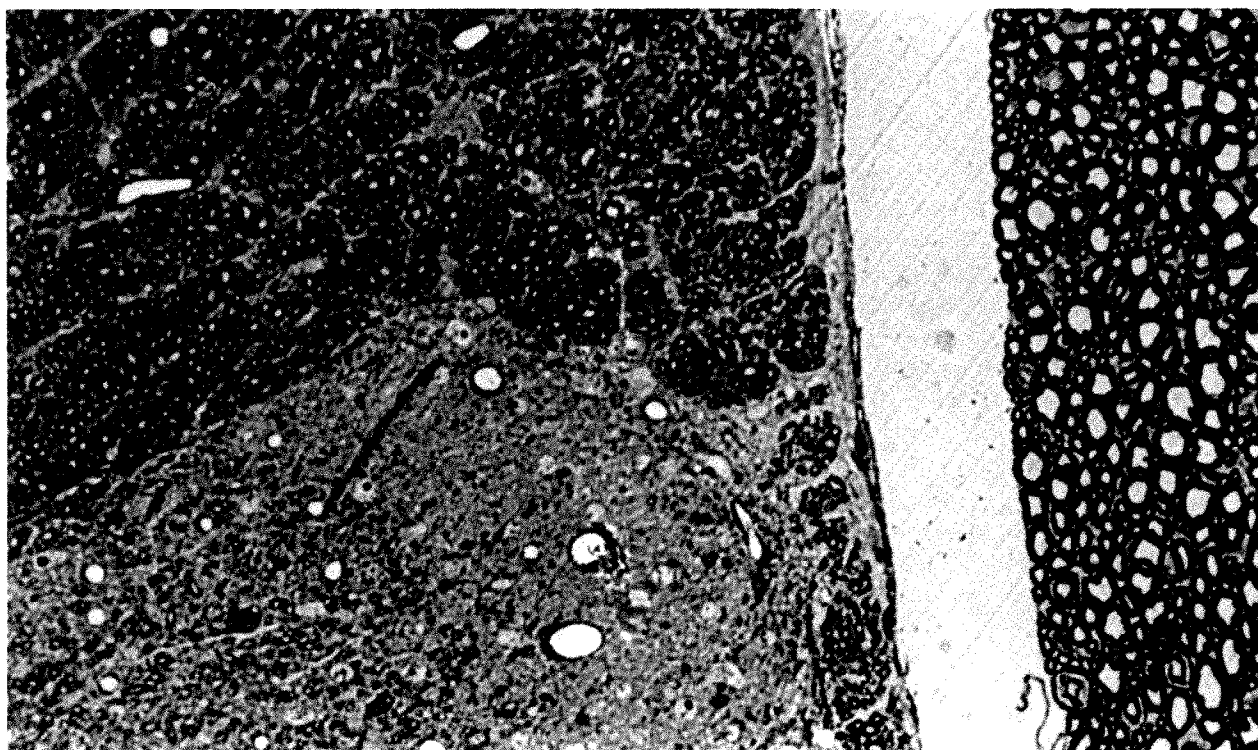


Figure 7. Dorsal horn and intradural part of nerve root from rat treated with guanfacine, 75 μ g, for 14 consecutive days. The structures appear normal. Toluidine blue stain.

administration of morphine was introduced clinically? (22) neurotoxicologic data were not available. Animal models for neurotoxicologic evaluation have been presented by different authors. Many methods have been tried, including either single intrathecal injections or chronically implanted intrathecal or epidural catheters (23-25).

The methods of neural tissue fixation, a crucial point in experimental neurotoxicologic studies, have varied. Paraformaldehyde immersion has been the standard technique in recent investigations of drug-induced spinal neurotoxicity (23-25). An example was published recently (26) of the results obtained with the paraformaldehyde-immersion technique in a study of the spinal neurotoxicity of cocaine. This technique resulted in swelling of the myelin, which may not be optimal for neurotoxicologic analysis of the long tracts.

In the present study we achieved good neural tissue fixation, which allowed detection of even minor neurotoxic lesions. In the animals treated with spartide, both normal and abnormal neurons were present side by side. The fixation produced by this method also supports the interpretation that the necrotic lesions caused by the substance P-antagonist are not caused by vascular occlusion, because the vessels appeared normal. Theoretically, however, intense but

transient vascular constriction in the grey matter could cause similar lesions. The mechanism of neurotoxicity thus merits further study. In addition, studies must be undertaken to determine whether the neurotoxic effect of spantide is specific to that particular agent, or if neurotoxicity is a common property of all substance P-antagonists.

When studying the sections by light microscopy, no differences were seen between the control groups and the groups treated with clonidine or guanfacine, even in the groups treated with high doses. There were no signs of general neuronal damage, or damage to particular cell types, indicative of a toxic effect. With regard to clonidine this finding agrees with the results of our earlier investigation, in which chronic intrathecal administration of clonidine to dogs did not result in neurotoxicity (15). The dorsal roots were selected for electron microscopic analysis because they have a large surface area exposed in the dural sac and are directly exposed to the test drugs. The small diameter in comparison with the spinal cord itself should allow good penetration by the test substances. A lesion in the dorsal root ganglia would be expected to show up in the dorsal roots (27). In most cases the dorsal horns were included in the sections. No signs of abnormal neural tissue were present.

One may argue whether morphological investigation is adequate to detect neurotoxic actions of spinally administered drugs, because such actions may be functional rather than structural. Clearly the ab-

sence of morphological change is not alone sufficient to free a drug from possible neurotoxic effects. Evaluation of a drug from a neurotoxicologic point of view should therefore be conducted as a combination of histopathological examination and functional studies as, e.g., in studies of spinal cord blood circulation (17) and of sensory evoked responses. However, findings from morphological studies, e.g., lesions in special cell types or locations, are important because the morphological basis of functional changes may then be detected. Lesions that do not produce clinical signs, i.e., subclinical states, may be of interest because they can forecast the kind of symptom that would occur if the lesion were more pronounced, and when functional neurologic compensation mechanisms are failing (28).

Data from pigs imply that epidural clonidine 3 μ g/kg does not affect spinal cord blood flow (17). This finding, the result of previous neurotoxicological investigations (15), plus the data resulting from the present study support the evidence that epidural clonidine is probably safe from a neurotoxicologic point of view for use in humans, although constant vigilance for detection of possible neurotoxic effects is necessary with the introduction of a new drug for spinal administration. In the clinical reports on spinal clonidine, no neurotoxic effects have yet been demonstrated (7-10). Concerning spinal guanfacine, further studies are recommended before it can be introduced into clinical practice.

In conclusion, we found in this light and electron microscopy study that clonidine and guanfacine, given intrathecally to rats daily for 14 days, gave rise to no detectable neurotoxic changes in the doses employed.

We gratefully acknowledge the help of Ewa Arweström, Madeleine Jarild, Gunilla Tibbling, and Christer Tengvar for advice and excellent technical assistance. We would also like to thank Boehringer Ingelheim and Sandoz for the supply of clonidine and guanfacine, respectively.

References

1. Yaksh TL. Pharmacology of spinal adrenergic systems which modulate spinal nociceptive processing. *Pharmacol Biochem Behav* 1985;22:845-58.
2. Yaksh T, Reddy SVT. Studies in the primate on the analgesic effects associated with intrathecal actions of opiates, alpha-adrenergic agonists and baclofen. *Anesthesiology* 1981;54:451-67.
3. Post C. Antinociceptive effects in mice after intrathecal injection of 5'-N-Ethylcarboxamide adenosine. *Neurosci Lett* 1984;51:325-30.
4. Plenory BJ, Tobias MA. Comparison of the antinociceptive activities of physostigmine, oxotremoridine and morphine in the mouse. *Br J Pharmacol* 1971;43:706-14.
5. Peterson J, Gordh TE Jr, Hartwig P, Wiklund L. A double blind trial of the analgesic effect of i.v. physostigmine on postoperative pain. *Acta Anaesthesiol Scand* 1986;30:283-8.
6. Chrubasik I, Maynadier I, Blond S. Somatostatin, a potent analgesic. *Lancet* 1984;ii:1208-9.
7. Goldstein JA. Clonidine as analgesic (Letter): *Biol Psychiatry* 1983; Nov 18:1339-40.
8. Gordh TE Jr, Tamsen A. A study on the analgesic effect of clonidine in man. *Acta Anaesthesiol Scand* 1983;27(Suppl 87):72.
9. Tamsen A, Gordh TE Jr. Epidural clonidine produces analgesia (Letter) *Lancet* 1984;11:231-2.
10. Coombs D, Saunders R, Lachance D, Savage S, Ragnarsson T, Jensen L. Intrathecal morphine tolerance: use of intrathecal clonidine, DADLE, and intraventricular morphine. *Anesthesiology* 1985;62:358-63.
11. Luttinger D, Ferrari R, Perrone MH, Haubrich DR. Pharmacological analysis of alpha-2-adrenergic mechanisms in nociception and ataxia. *J Pharmacol Exp Ther* 1985;232,3:883-9.
12. Howe JR, Jia-Yi Wang, Yaksh TL. Selective antagonism of the antinociceptive effect of intrathecally applied alpha-adrenergic agonists by intrathecal prazosin and intrathecal yohimbine. *Pharmacol Exp Ther* 1983;224(no 3):552-8.
13. Probst A, Cortés R, Palacios M. Distribution of α -2-adrenergic receptors in the human brainstem: an autoradiographic study using (³H)p-aminoclonidine. *Eur J Pharmacol* 1984;106:477-88.
14. Marwaha I, Kehne J, Commisaris R, Lakoski I, Shaw W, Davi M. Spinal clonidine inhibits neural firing in locus coeruleus. *Brain Res* 1983;276:379-82.
15. Gordh TE Jr, Ekman S, Lagerstedt AS. Evaluation of possible spinal neurotoxicity of clonidine. *Ups J Med Sci* 1984;89:266-73.
16. Tamsen A, Gordh TE Jr. Clonidine is not neurotoxic (Letter) *Lancet* 1984;ii:876.
17. Gordh TE Jr, Feuk U, Norlén K. Effect of epidural clonidine on spinal cord blood flow, and regional and central hemodynamics in pigs. *Anesth Analg* 1986;65:1312-8.
18. Gordh TE Jr, Hartwig P. CSF and plasma concentrations of clonidine in the pig after epidural i.v. and i.m. administration (In press, *Ups J Med Sci* 1986).
19. Yaksh TL, Rudy TA. Chronic catheterization of the spinal subarachnoid space. *Physiol Behav* 1976;17:1031-6.
20. Post C, Paulsson I. Antinociceptive and neurotoxic actions of substance P-analogues in the rat's spinal cord after intrathecal administration. *Neurosci Lett* 1985;57:159-164.
21. Källskog Ö, Lindblom LO, Ulfvëndahl HR. Regional and single glomerular blood flow in the rat kidney prepared for micropuncture. *Acta Physiol Scand* 1975;94:145-53.
22. Bahar M, Olshwang D, Kagora F, Davidson JT. Epidural morphine in the treatment of pain. *Lancet* 1979;ii:527-9.
23. Kytä I, Rosenberg PH, Wahlström T. Histopathological change in the rabbit spinal cord caused by bupivacaine. *Acta Anaesthesiol Scand* 1981;72(suppl 25):38.
24. Bahar M, Rosen M, Vickers MD. Chronic cannulation of the intradural or extradural space in the rat. *Br J Anaesth* 1984;56:405-10.
25. Ravindran R, Turner M, Muller J. Neurologic effects of subarachnoid administration of 2-chloroprocaine CE, bupivacaine and low pH normal saline in dogs. *Anesth Analg* 1982;61:279-8.
26. Bahar M, Cole G, Rosen M. Histopathology of the spinal cord after intrathecal cocaine, bupivacaine, lignocaine and adrenaline in the rat. *Eur J Anaesth* 1984;1:293-7.
27. Treip CS. *Neuropathology*: London: Wolfe Medical Publishing 1978:9.
28. Spencer P, Bischoff M, Schaumburg H. Neuropathologic methods for the detection of neurotoxic disease. In: *Experimental and clinical neurotoxicology*. Baltimore: Williams & Wilkins, 1980:743-56.

Effect of Epidural Clonidine on Spinal Cord Blood Flow and Regional and Central Hemodynamics in Pigs

Torsten Gordh Jr, MD, Ulla Feuk, MD, and Karin Norlén, MD, PhD

GORDH T, FEUK U, NORLÉN K. Effect of epidural clonidine on spinal cord blood flow and regional and central hemodynamics in pigs. *Anesth Analg* 1986; 65:1312-8.

Epidural clonidine is reported to produce analgesia in humans. To investigate the effect of epidural injection of the α_2 -adrenoceptor agonist on spinal cord blood flow as well as on regional and central blood flow and hemodynamics, 11 anesthetized pigs were studied. Each pig received clonidine in increments of 3, 10 and 30 $\mu\text{g/kg}$, each dose given in a volume of 5 ml via a lumbar epidural catheter. The tip of the catheter was located in the lumbar epidural space. The microsphere method was used to measure regional circulation. The measurements were made 45 min after each dose. Each pig served as its own control. The lowest dose of epidural clonidine (3 $\mu\text{g/kg}$) did not affect regional blood

flow to the spinal cord or to any other organ. The intermediate and high doses were associated with local vasoconstriction in the lumbar and thoracic parts of the spinal cord that produced a statistically significant reduction in flow of 25-35% ($P < 0.05$). Blood flow to the brain, cerebellum and the cervical parts of the spinal cord was not significantly changed, nor was renal blood flow. In the adrenal and in skeletal muscles a marked reduction of the blood flow occurred after the high dose, 61% and 78%, respectively. These findings indicate that epidural clonidine 3 $\mu\text{g/kg}$, a dose of clinical interest, is not likely to produce dangerous vasoconstriction in the spinal cord.

Key Words: SYMPATHETIC NERVOUS SYSTEM, α -AGONISTS—clonidine. SPINAL CORD, BLOOD FLOW—clonidine.

An antinociceptive effect has been demonstrated in animals after the systemic and intrathecal administration of the α_2 -adrenoceptor agonist clonidine (1,2). This effect is reversed by α_2 -adrenoceptor antagonists but not by naloxone, indicating a mechanism of action different from that of opioids (3). Analgesia has been reported after intravenous (IV) administration of clonidine to patients suffering from postoperative pain (4), after epidural injection of clonidine in patients with severe neurogenic pain (5), and after intrathecal administration in patients suffering from intractable pain associated with malignancies (6). The mechanism of action of epidural or intrathecal clonidine analgesia is considered to be activation of the postsynaptic α_2 -adrenoceptors (7) in the substantia gelatinosa in the spinal cord (8). Supraspinal effects of clonidine may also contribute to its analgesic effects (9). Spinal clonidine analgesia is not associated with

disturbances of motor function (10). As with epidural morphine, the epidural route of administration of clonidine may be more suitable than the systemic parenteral route, because high concentrations of the drug appear in the cerebrospinal fluid close to the site of action (11).

Prior to more widespread use of epidural clonidine, data about spinal neurotoxicity should be obtained. Limited information has been reported. Dogs and rats treated with high doses of intrathecal clonidine through indwelling catheters for 14 days showed no signs of neurotoxicity (12,13).

Studies of the effects of spinally administered drugs on blood flow in the spinal cord have been suggested as a part of their toxicological assessment (14). On a theoretical basis such studies are especially necessary for the epidural or intrathecal use of α -receptor agonist drugs, because these may well produce a local vasoconstriction by stimulating vascular smooth muscle α -receptors (15) and thus may produce potentially dangerous decreases in spinal cord blood flow. The present study was designed to assess the effect of clonidine on spinal cord blood flow after epidural administration of clonidine in pigs. Changes in the regional blood flow of the brain and other organs were also studied, as well as central hemodynamic effects.

This work was supported by grants from the Bank of Sweden Trecentenary Foundation (81/120, A. Tamsen) and from Boehringer Ingelheim Co, Sweden.

Received from the Department of Anaesthesiology, University Hospital, Uppsala, Sweden. Accepted for publication July 26, 1986.

Address correspondence to Dr. Gordh, Department of Anaesthesiology, University Hospital, S-751 85 Uppsala, Sweden.

Materials and Methods

After approval by our Committee on Animal Research, eleven pigs of Swedish breed, weighing 20–23 kg, were used. The pigs were prepared for the study using the techniques described below.

Basal Anesthesia and Ventilation

Anesthesia was induced with ketamine (Ketalar^R), 500 mg IV. Atropine, 0.5 mg, was also given IV. A tracheostomy was performed, and the lungs ventilated with a volume controlled ventilator (Servo 900B, Siemens Elema, Sweden) at a frequency of 20 breaths per minute with the tidal volume adjusted to achieve normocapnia. Anesthesia was maintained with 30% oxygen in nitrous oxide during the surgical preparation. A continuous infusion containing methomidate, 0.5 g/L, (Hypnodil^R) and pancuronium bromide, 12 mg/L, (Pavulon^R) in 1000 ml glucose, 25 mg/ml, in saline (Rehydrex^R) was given throughout the experiment at a rate of $10 \text{ ml} \cdot \text{kg}^{-1} \cdot \text{hr}^{-1}$. After completing the surgical preparation, the animals were ventilated with air.

Surgical Preparation

Catheters for pressure measurements, blood sampling and infusions were placed in the right atrium via the left jugular vein, in the pulmonary artery, and in the right carotid artery. The position of the pulmonary artery catheter was verified by pressure recordings. The left carotid artery was cannulated and a catheter for microsphere injection was advanced into the left ventricle of the heart as verified by pressure recordings. A small superficial branch of the femoral artery was cannulated, to be used for aspiration of a reference sample according to the microsphere technique.

Epidural Injection

The first or second lumbar interspace was identified and the epidural space located with the loss of resistance technique. An epidural catheter was introduced and advanced 5 cm. The position of the catheter was later verified at autopsy.

Blood Pressures and Heart Rate

Arterial, pulmonary arterial, and pulmonary capillary wedge pressures were measured. Central venous pressure (CVP) was measured through the proximal lumen of the pulmonary arterial catheter. The cath-

eters were connected to pressure transducers, and the signals were recorded on a multichannel ink-jet recorder (Mingograf 81, Elema-Schönander, Sweden). Heart rate was determined from the pressure recording.

Cardiac Output

Cardiac output was calculated using both the microsphere (CO_{sf}) and thermodilution (CO_{T}) techniques, the latter by a cardiac output computer (Cardiac output computer 9520, Edwards Lab, CA,). The mean of five measurements was calculated.

Blood Gases and Acid-Base Status

Blood gas tensions and acid-base status were measured using an ABL-1 autoanalyzer (Radiometer, Copenhagen, Denmark). The body temperature was measured with a thermistor in the pulmonary artery. A radiant heat lamp was used to maintain body temperature.

Microsphere Method and Regional Blood Flow

Regional blood flows and cardiac output were measured with the microsphere technique (17). In summary, radiolabelled microspheres, which are too large to pass through the capillary system, are injected into the circulation and used to measure blood flow by comparing tissue radioactivity with the radioactivity of an arterial blood sample withdrawn at a known flow rate during the injection and distribution of the spheres. Using spheres with different isotope labels, serial flow measurements can be made in the same animal. In this study, the microspheres were injected into the left ventricle.

The reference sample was drawn from a small superficial branch of the femoral artery, using a motor syringe at a rate of 1.2 ml/min (Sage Instrument Syringe, pump 352). The syringe served as a reference organ when calculating blood flows. Carbonized microspheres of $15 \pm 1 \mu\text{m}$, dissolved in 0.9% saline (3M Co., St Paul, MN) and labelled with ^{141}Ce , ^{51}Cr , ^{85}Sr , or ^{95}Nb , were used. Blood flow could therefore be measured on four occasions in the same animal. Immediately before injection $2\text{--}3 \times 10^6$ microspheres were suspended in fresh pig plasma to a total volume of 1 ml and agitated in a Vortex JR Mixer. The different microspheres were given alternatively to avoid systematic errors.

At autopsy, specimens measuring 1 ml were taken from heart (septum, right and left ventricle), lung (hilus, upper and lower lobes), cerebrum and cerebellum (equal amounts of grey and white matter), and

Table 1. Hemodynamic Data and Arterial Blood Gas Tensions

Variable	Clonidine dose			
	Baseline values (n = 11)	3 ($\mu\text{g/kg}$) (n = 11)	10 ($\mu\text{g/kg}$) (n = 11)	30 ($\mu\text{g/kg}$) (n = 10)
HR (min)	144 \pm 34	116 \pm 23 ^b	95 \pm 17 ^c	93 \pm 30 ^c
CO _T (L/min)	3.7 \pm 0.40	3.1 \pm 0.43 ^c	2.7 \pm 0.56 ^c	2.6 \pm 0.59 ^c
CO _{af} (L/min)	3.3 \pm 0.60	2.6 \pm 0.45 ^a	2.2 \pm 0.73 ^b	2.1 \pm 0.40 ^b
SV (ml)	24 \pm 0.7	23 \pm 0.5	22 \pm 0.7	22 \pm 0.5
MAP (mm Hg)	116 \pm 13	114 \pm 17	101 \pm 8 ^b	109 \pm 18
CVP (mm Hg)	1.5 \pm 1.91	1.8 \pm 1.47	1.9 \pm 1.10	2.8 \pm 1.22 ^a
MPAP (mm Hg)	17.9 \pm 5.82	19.9 \pm 6.5	18.7 \pm 4.9	24.0 \pm 6.3 ^c
MPCWP (mm Hg)	5.6 \pm 2.25	7.1 \pm 2.28	5.9 \pm 1.74	7.6 \pm 2.31
SVR (mm Hg·L ⁻¹ ·min)	31.8 \pm 5.07	37.8 \pm 8.14 ^a	38.5 \pm 10.00 ^a	42.2 \pm 9.71 ^b
PaO ₂ (mm Hg)	106 \pm 22.5	105 \pm 22.2	106 \pm 24.7	113 \pm 24.8
Paco ₂ (mm Hg)	38 \pm 5.6	35 \pm 3.6	35 \pm 3.1	35.3 \pm 2.1
pH	7.44 \pm 0.07	7.46 \pm 0.04	7.49 \pm 0.04	7.49 \pm 0.05
BE (mmol/L)	1.6 \pm 3.37	2.1 \pm 3.35	3.4 \pm 2.57 ^a	4.0 \pm 2.75
Hematocrit (%)	33 \pm 1.5	32 \pm 1.9	31 \pm 1.7	32 \pm 2.3
Blood temperature _(O₂) (°C)	37.8 \pm 0.75	37.7 \pm 0.79	37.4 \pm 0.96	37.2 \pm 0.86

Values are mean \pm SD. The measurements were made 45 min after each incremental dose of epidural clonidine. Each value is compared to baseline value using Student's *t*-test for paired samples.

Abbreviations: HR, heart rate; CO_T, cardiac output determined by thermodilution; CO_{af}, cardiac output determined by microsphere method; SV, stroke volume; MAP, mean arterial pressure; CVP, central venous pressure; MPAP, mean pulmonary arterial pressure; MPCWP, mean pulmonary capillary wedge pressure; SVR, systemic vascular resistance; BE, base excess.

^a*P* < 0.05. ^b*P* < 0.01. ^c*P* < 0.001.

the whole spinal cord. The cord was divided into cervical, thoracic, and lumbar (including sacral) segments. Specimens were also taken from both kidneys, both adrenals, pancreas, liver, spleen, stomach, small bowel, and skeletal muscle (foreleg, hindleg and i-eopsoas).

The specimens and the reference samples were analyzed for their content of ¹⁴¹Ce, ⁵¹Cr, ⁸⁵Sr, and ⁹⁵Nb in a gammaspectrophotometer (Nuclear Chicago, 10871. Correction was made for overlap between the isotopes. The total amount of radioactivity injected was determined from the difference between the radioactivity in the syringe before and after the injection.

Calculations

The regional blood flows to the various organs, QE, in ml·min⁻¹·g⁻¹, were calculated as $QR = (\text{organ activity} \times \text{reference sample flow}) / \text{reference sample activity}$. Cardiac output (CO_{af}) was determined using the formula $CO_{af} = (\text{total injected activity} \times \text{reference sample flow}) / (\text{reference sample activity})$. The vascular resistance of the systemic circulation (SVR) and of the different organs were calculated according to the formula $(MAP - MPAP) / (\text{blood flow})$. Each animal served as its own control.

Doses of Clonidine

Clonidine (Catapressan^R) was injected into each animal in increments of 3 (low dose), 10 (intermediate

dose), and 30 (high dose) $\mu\text{g/kg}$ through the epidural catheter. One hour elapsed between the doses. Thus, each animal received a total of 43 $\mu\text{g/kg}$ of clonidine during the experiment. Each dose was given in 5 ml of vehicle. The low dose is in the dose range reported to produce analgesic effects after epidural administration in man (5). The two higher doses exceed clinical dosages.

Experimental Procedure

After preparation the animals were allowed to stabilize for 45 min while ventilated with air. Baseline measurements were made of the mean arterial pressure (MAP), mean pulmonary arterial pressure (MPAP), mean pulmonary capillary wedge pressure (MPCWP), cardiac output (CO_T), and heart rate (HR). Blood samples for measurement of hematocrit, arterial blood gas tensions, and acid-base status were collected. Microspheres were then injected into the left ventricle. The blood pressure and CO_T measurements were repeated immediately after the injection of the microspheres. These measurements constituted the baseline values, to which the changes induced by epidural administration of clonidine were compared. After completing the baseline measurements, clonidine, 3 $\mu\text{g/kg}$, was injected epidurally. Forty-five minutes after this injection the measurements were repeated and the second microsphere injection was carried out. The third and fourth set of recordings were made 45 min after the animal had received clo-

Table 2. Central Nervous System Blood Flows and Vascular Resistances

Organ	Blood flows (ml·min ⁻¹ ·g ⁻¹)				Organ resistances (mm Hg·ml ⁻¹ ·min·g)			
	Baseline values	Epidural clonidine (μg/kg)			Baseline values	Epidural clonidine (μg/kg)		
		3 (n = 11)	10 (n = 11)	30 (n = 10)		3 (n = 11)	10 (n = 11)	30 (n = 10)
Cervical spinal cord	0.18 ± 0.07	0.18 ± 0.07	0.16 ± 0.05	0.13 ± 0.03 ^a	713 ± 229	669 ± 163	716 ± 274	887 ± 231
Thoracic spinal cord	0.20 ± 0.04	0.18 ± 0.04	0.16 ± 0.05	0.13 ± 0.03 ^b	634 ± 213	669 ± 163	715 ± 274	887 ± 230 ^a
Lumbar spinal cord	0.24 ± 0.08	0.22 ± 0.04	0.18 ± 0.04 ^b	0.17 ± 0.03 ^b	520 ± 144	524 ± 108	558 ± 118 ^a	636 ± 134 ^a
Cerebrum	0.36 ± 0.11	0.40 ± 0.12	0.36 ± 0.07	0.34 ± 0.07	341 ± 91	310 ± 108	292 ± 77	324 ± 66
Cerebellum	0.42 ± 0.16	0.44 ± 0.14	0.43 ± 0.15	0.35 ± 0.08	301 ± 96	277 ± 90	254 ± 79	314 ± 93

All values are mean ± SD. The measurements were made 45 min after each incremental dose of epidural clonidine. Each value is compared to baseline value, using Student's *t*-test for paired samples.

^a*P* < 0.05.

^b*P* < 0.01.

nidine epidurally at the doses of 10 and 30 μg/kg respectively. The animals were killed by an intracardiac injection of KCl and tissue specimens for measurements of regional blood flow were collected.

Statistics

The values are presented as means ± standard deviation. Statistical analysis was performed using two-tailed Student's *t*-test for paired data to compare the baseline values with values measured 45 min after the epidural administration of 3, 10, and 30 μg/kg of clonidine, respectively. Statistical significance was presumed when *P* ≤ 0.05.

Results

One pig died because of technical problems in ventilation before the fourth set of measurements was completed. The values obtained after the different doses of clonidine were compared with baseline values. No significant changes occurred in arterial oxygen and carbon dioxide tensions, acid-base status, body temperature or hematocrit during the experiment (Table 1).

Hemodynamic Effects

Central blood pressures. Mean arterial blood pressure was unchanged after the low dose of epidural clonidine. After the intermediate dose a moderate, but statistically significant, reduction to 101 from 116 mm Hg occurred. After the high dose of clonidine, MAP increased to 109 mm Hg. Central venous pressure and MPAP increased significantly only after the highest clonidine dose. MPCWP did not change (Table 1).

Systemic perfusion pressure (MAP – CVP) decreased slightly but statistically significantly (13%) only after the intermediate dose.

Cardiac output, heart rate, and stroke volume. Cardiac output (CO_T) decreased significantly after epidural clonidine, to 3.1 from 3.7 L/min (16%) after the low dose, and to 2.7 and 2.6 L/min (27% and 30%) after the intermediate and high doses, respectively. Heart rate also decreased significantly after each dose of epidural clonidine, from 144 to 116 to 95 to 93 beats/min, respectively. Stroke volume (SV) did not change. The CO_{st} values were 15–20% lower than the values obtained with thermodilution technique (Table 1).

Systemic vascular resistance. The systemic vascular resistance increased significantly after all clonidine doses, from 31.8 to 37.8 mm Hg·L⁻¹·min⁻¹ after the low dose, to 38.5 after the intermediate, and to 42.5 after the high dose (Table 1).

Organ Regional Blood Flows and Vascular Resistances

Spinal cord, cerebrum, and cerebellum. Epidural clonidine in the dose of 3 μg/kg did not affect blood flow in any part of the spinal cord. After 10 μg/kg the flow was unchanged in the cervical and thoracic parts of the cord, whereas it decreased significantly in the lumbar part to 18 from 24 ml·min⁻¹·g⁻¹ (25%). After the high dose of clonidine, 30 μg/kg, a significant decrease of the blood flow was observed in both the thoracic (35%) and the lumbar (29%) parts of the spinal cord. The decrease in blood flows was associated with a significant increase in the spinal cord vascular resistances (Table 2). In the cerebrum and cerebellum no significant changes occurred in regional blood flow or organ vascular resistances despite a decrease in CO (Table 2).

Table 3. Organ Blood Flows and Organ Vascular Resistances

Organ	Blood flows (ml·min ⁻¹ ·g ⁻¹)				Organ resistances (mm Hg·ml ⁻¹ ·min·g)			
	Baseline values (n = 11)	Epidural clonidine (μg/kg)			Baseline values	Epidural clonidine (μg/kg)		
		3 (n = 11)	10 (n = 11)	30 (n = 10)		3 (n = 11)	10 (n = 11)	30 (n = 10)
Heart	1.49 ± 0.52	1.20 ± 0.24	0.84 ± 0.33 ^b	0.83 ± 0.22 ^b	96 ± 48	100 ± 33	138 ± 58 ^b	133 ± 34
Lung (AV shunt flow)	0.82 ± 0.40	0.78 ± 0.47	0.96 ± 0.76	0.80 ± 0.65	—	—	—	—
Kidney	2.33 ± 0.79	2.43 ± 0.27	2.40 ± 0.59	2.27 ± 0.45	544 ± 176	474 ± 99	437 ± 118	487 ± 136
Suprarenal gland	2.56 ± 1.04	2.27 ± 0.85	1.24 ± 0.43 ^b	0.99 ± 0.27 ^b	51 ± 17	58 ± 28	95 ± 53 ^a	113 ± 28 ^c
Pancreas	0.45 ± 0.20	0.62 ± 0.31	0.65 ± 0.26 ^a	0.70 ± 0.34	329 ± 214	230 ± 140	181 ± 90	195 ± 103
Liver (hepatic artery)	0.34 ± 0.17	0.24 ± 0.14	0.19 ± 0.24 ^a	0.15 ± 0.10 ^a	472 ± 352	753 ± 619	1229 ± 922 ^a	1035 ± 869 ^a
Spleen	2.61 ± 0.92	2.61 ± 1.09	1.96 ± 0.43 ^a	2.48 ± 0.96	51 ± 24	48 ± 15	53 ± 15	46 ± 11
Stomach	0.20 ± 0.10	0.20 ± 0.09	0.24 ± 0.19	0.23 ± 0.14	764 ± 445	651 ± 283	543 ± 231	585 ± 278
Small bowel	0.45 ± 0.16	0.49 ± 0.16	0.38 ± 0.09	0.31 ± 0.09 ^a	292 ± 111	252 ± 85	276 ± 69	584 ± 278
Muscle	0.18 ± 0.06	0.19 ± 0.12	0.05 ± 0.02 ^c	0.04 ± 0.01 ^c	720 ± 261	896 ± 648	2434 ± 1170 ^c	2887 ± 867 ^c

Values are mean ± SD. The measurements were made 45 min after each incremental dose of epidural clonidine. Each value is compared to baseline value using Student's *t*-test for paired samples.

^a*P* < 0.05.

^b*P* < 0.01.

^c*P* < 0.001.

Other organs. Myocardial blood flow decreased significantly after the intermediate and high doses (40% and 41% respectively) in association with a significant increase in coronary vascular resistance. In the kidneys blood flow was maintained in spite of the decrease in cardiac output. Blood flows to the right and left kidneys were similar, indicating an adequate mixing between the microspheres and the blood. In the adrenal glands a marked decrease in blood flow occurred after the intermediate and the high doses of clonidine (52% and 61%, respectively) along with increases in organ vascular resistance. The pancreatic blood flow increased slightly. In the spleen a 25% decrease in blood flow occurred only after the intermediate clonidine dose. In the small bowel a 31% decrease was seen in blood flow after the high dose of clonidine. Stomach blood flow was unchanged.

In muscle no change occurred in blood flow after 3 μg/kg of clonidine. After the two higher doses, a marked reduction of blood flow occurred (72% and 78%, respectively) as organ vascular resistance increased. In the lungs, where the measured flow represents the magnitude of microspheres bypassing the systemic capillary system through arteriovenous shunts in addition to the flow from the bronchial arteries, no significant changes occurred. In the liver the microsphere technique gives information about the flow from the hepatic artery only. A significant decrease in blood flow, as well as an increase of the hepatic artery vascular resistance, took place after the higher doses.

Discussion

The Microsphere Method

Variability of the microsphere method is determined by the number of spheres in the samples; for practical purposes 400 microspheres per sample has been considered sufficient to allow reasonable precision (17). Injection of 2–3 × 10⁶ microspheres in pigs gives at least this number of spheres in the reference sample. The number of microspheres may be smaller in organs with blood flow values of 0.1 ml·min⁻¹·g⁻¹ or less. However, this reduction can be compensated for by increasing the number of tissue samples (17). The blood flow in the spinal cord is above this critical value, and in this experiment the whole spinal cord was taken for analysis. Therefore, the microsphere method used here should allow adequate measurement of spinal cord blood flow.

Hemodynamic Changes

The baseline values are in accordance with the values reported by other investigators using the microsphere method in pigs (18). The difference between CO_{sf} and CO_T of about 15–20% found in this investigation is in accordance with a study in which CO values obtained with microspheres and with thermodilution were compared (19). In the present study, physiological parameters such as ventilatory and acid-base status, hematocrit, and body temperature remained constant during the experiment. In other experiments per-

formed by our group, using the same experimental design in studying regional blood flow in pigs, we have found no marked reduction of CO and HR, nor a tendency towards increased organ vascular resistances in spinal cord, skeletal muscle, or adrenal glands (K. Norlén, unpublished data). The observed circulatory changes could therefore be attributed to the epidural administration of clonidine.

The decrease in CO was due to a reduction in heart rate. Clonidine has a documented negative chronotropic effect in higher doses (20). Mean arterial pressure and the perfusion pressure decreased significantly only after the intermediate clonidine dose. Further reduction of MAP could be anticipated using an antihypertensive drug like clonidine, but in high-dose levels clonidine acts as an α -receptor agonist in the peripheral vascular bed to produce vasoconstriction that may counteract reduction in MAP (15). Vascular absorption from the epidural and subarachnoid spaces, and subsequent action on the peripheral vasculature, may explain the increases in SVR and MAP seen after the high dose of clonidine. Systemic vascular resistance increased significantly even after the low dose, but a compensatory increase in SVR because of the decreased CO may also add to this.

Changes in Regional Blood Flow in Central Nervous System

After the low dose of clonidine, 3 $\mu\text{g/kg}$, no change in regional blood flow or vascular resistance occurred in the central nervous system (CNS). This dose is of clinical interest. After the intermediate and high doses of clonidine, vasoconstriction occurred in the lumbar and thoracic parts of the spinal cord, reducing the blood flow 25–35%. The perfusion pressure was unchanged after the high dose, and only slightly decreased after the intermediate, which indicates that autoregulation of spinal cord blood flow was overruled by a direct local vasoconstrictive effect of clonidine, probably caused by α -receptor agonism. In addition, the repeated injections of 5 ml of fluid in the epidural space may cause some of the changes seen in spinal cord blood flow. Epidurally administered clonidine is present in high concentrations in the cerebrospinal fluid (CSF) after 20 min. At that time the plasma concentration of clonidine is very low (21). Because the drug was injected into the lumbar epidural space, it can be assumed that the local CSF concentration of clonidine was highest around the caudal parts of the cord, where the vasoconstriction occurred.

The reduction in regional blood flow in the lower

parts of the spinal cord were of the same relative magnitude as the decrease in CO, but this reduction in CO did not cause significant reduction of regional blood flow in the cervical parts of the spinal cord, cerebrum, or cerebellum. This pattern indicates that the reduced CO is distributed to the CNS and other organs such as the kidney given priority. The redistribution of CO is probably achieved by vasoconstriction in peripheral organs. The data concerning the CNS-vasoconstrictive effects of clonidine are conflicting. Earlier findings that IV clonidine, 2 $\mu\text{g/kg}$, in man produced a decrease in cerebral blood flow of 30% of baseline values (22) could not be confirmed in the present study, even after high doses of clonidine. In vitro clonidine (up to 10^{-5} M) applied locally to monkey cerebral vessels does not produce vasoconstriction (23).

Changes in Regional Blood Flow in Other Organs

Renal blood flow was maintained in spite of the reduction in CO. Pancreatic blood flow increased slightly. In other organs a tendency towards vasoconstriction was seen after the intermediate and high doses of clonidine. The vasoconstrictive actions probably represent an extraspinal effect of clonidine on α -receptors in the vascular smooth muscle in these organs (24). In the adrenal glands the blood flow was markedly reduced after the higher clonidine doses, which may be due to a direct vasoconstrictive action of clonidine. An alternative explanation is that clonidine decreased the outflow from the sympathetic nervous system (25) which may decrease neurogenic stimulation of the adrenals (26), causing decreased metabolic activity and hence decreasing blood flow. Methomidate, used for anesthesia in this study, may also affect adrenal blood flow, because etomidate, an anesthetic drug closely chemically related to methomidate, produces a significant depression of adrenal function (27).

In the skeletal muscles a pronounced vasoconstriction occurred after the high clonidine doses. This effect can be explained by a direct α -agonist effect on vascular smooth muscle (28) where vasoconstrictive α_2 -adrenoceptors are found extrajunctionally, and affected mainly by circulating catecholamines (28). Postsynaptic vasoconstrictive α_1 -adrenoceptors have also been demonstrated near the neuroeffector junction of vascular smooth muscle, being stimulated mainly by sympathetic nerve activity (28). In humans, however, IV clonidine may increase or decrease discharge in muscular sympathetic nerves (29). The pronounced increase of SVR in our study was most likely caused mainly by the vasoconstriction in the muscles. The

oxygen delivery to the muscles probably remained sufficient, because no metabolic acidosis occurred. The effects of clonidine on regional blood flow obviously vary depending on the dose, route of administration, and the organ studied.

In this study, no potentially harmful effects were found after 3 $\mu\text{g/kg}$ of epidural clonidine. Previous morphologic investigations of spinal neurotoxicity after chronic intrathecal clonidine in dogs and rats also have shown no neurotoxic effects (12,13). These findings taken together indicate that epidural clonidine is probably safe to use in man from a neurotoxicologic point of view, although vigilance must be high concerning neurologic side effects when introducing a new drug for spinal use into clinical practice.

In conclusion, we found that clonidine administered epidurally to pigs in a dose of 3 $\mu\text{g/kg}$ had no effect on spinal cord blood flow or the regional blood flow to any other organ. After doses above 10 $\mu\text{g/kg}$, significant reductions of the blood flow in the spinal cord were found, caused by a local vasoconstriction.

We gratefully acknowledge the help of Anders Alvfors, BS, for excellent technical assistance.

References

- Paalzow L. Analgesia produced by clonidine in mice and rats. *J Pharm Pharmacol* 1974;26:361-3.
- Reddy SVR, Maderdrut JL, Yaksh TL. Spinal cord pharmacology of adrenergic agonist mediated antinociception. *J Pharmacol Exp Ther* 1980;213(3):525-33.
- Yaksh T, Reddy SVT. Studies in the primate of the analgesic effects associated with intrathecal actions of opiates, alpha-adrenergic agonists and baclofen. *Anesthesiology* 1981;54:451-67.
- Gordh TE Jr, Tamsen A. A study on the analgesic effect of clonidine of man. *Acta Anaesthesiol Scand* 1983;27(suppl 87):72.
- Tamsen A, Gordh TE Jr. Epidural clonidine produces analgesia. (Letter) *Lancet* 1984;ii:231-2.
- Coombs D, Saunders R, Lachance D, Savage S, Ragnarsson T, Jensen L. Intrathecal morphine tolerance: use of intrathecal clonidine, DADLE, and intraventricular morphine. *Anesthesiology* 1985;62:358-63.
- Howe JR, Wang JY, Yaksh TL. Selective antagonism of the antinociceptive effect of intrathecally applied alpha adrenergic agonists by prazosin and intrathecal yohimbine. *J Pharmacol Exp Ther* 1983;224:552-8.
- Probst A, Cortés R, Palacios M. Distribution of α -2-adrenergic receptors in the human brainstem—an autoradiographic study using (^3H)p-amino-clonidine. *Eur J Pharmacol* 1984;106:477-88.
- Marwaha J, Rehne J, Commisaris R, Lakoski J, Shaw W, Davis M. Spinal clonidine inhibits neural firing in locus coeruleus. *Brain Res* 1983;276:379-82.
- Yaksh TL. Pharmacology of spinal adrenergic systems which modulate spinal nociceptive processing. *Pharmacol Biochem Behav* 1985;22:845-58.
- Gustafsson L. Spinal opiate analgesia: clinical and experimental aspects. (Thesis). Stockholm: Karolinska Institute, 1985:46.
- Gordh TE Jr, Ekman S, Lagerstedt AS. Evaluation of possible spinal neurotoxicity of clonidine. *Ups J Med Sci* 1984;89:266-73.
- Gordh TE Jr, Post C, Olsson Y. Toxicity testing of clonidine, guanfacine and a substance P-antagonist on rat spinal cord and nerve roots. *Anesth Analg* 1986;65:1303-11.
- Yaksh TL. Effects of spinally administered agents on spinal cord blood flow. A need for further studies. *Anesthesiology* 1983;59:173-5.
- Hoefke W. Clonidine. In: Scriabine A, ed. *Pharmacology of antihypertensive drugs*. New York: Raven Press, 1980:55-87.
- Heymann MA, Payne BD, Hoffman JIE, Rudolph AM. Blood flow measurements with radio-nuclide-labeled particles. *Prog Cardiovasc Dis* 1977;20:55-79.
- Buckberg GD, Luck JC, Payne DB, Hoffman JIE, Archie JP, Fixler DE. Some sources of error in measuring regional blood flow with radioactive microspheres. *J Appl Physiol* 1971;31:598-604.
- Haldén E. Circulatory and ventilatory effects of increased airway pressure (Dissertation). Uppsala, Sweden: University of Uppsala, 1980.
- Archie JP, Fixler DE, Ulliyot DJ, Hoffman JIE, Utley JR, Carlson EL. Measurement of cardiac output with an organ trapping of radioactive microspheres. *J Appl Physiol* 1973;35:148-54.
- de Jonge A, Timmermans PBMW, van Zweiten PA. Participation of cardiac presynaptic α_2 -adrenoceptors in the bradycardic effects of clonidine and analogues. *Naunyn Schmiedeberg Arch Pharmacol* 1981;317:8-12.
- Gordh TE Jr, Hartvig P. CSF and plasma concentrations of clonidine in pigs after epidural i.v. and i.m. administration. In press, *Ups J Med Sci* 1986.
- James M, Larbi E, Zaimis E. The effect of the acute intravenous administration of clonidine (St 155) on cerebral blood flow in man. *Br J Pharmacol* 1970;39:198-9.
- Toda N. Alpha adrenergic receptor subtypes in human, monkey and dog cerebral arteries. *J Pharmacol Exp Ther* 1983;266:861-8.
- Yasuoka S, Yaksh TL. Effects on nociceptive threshold and blood pressure of intrathecally administered morphine and α -adrenergic agonists. *Neuropharmacology* 1983;22:309-15.
- Werner N. Drugs that inhibit adrenergic nerves and block adrenergic receptors. In: Goodman Gilman A, Goodman LS, Rall TW, Murad F, eds. *The pharmacological basis of therapeutics*. 7th ed. New York: MacMillan Publishing Co. 1986:181-214.
- Guyton AC. *Textbook of medical physiology*, 4th ed. Philadelphia, WB Saunders Co, 1986:692-3.
- Wagner LR, White PF. Etomidate inhibits adrenocortical function in surgical patients. *Anesthesiology* 1984;61:647-51.
- Matthews WD, Jim KF, Hieble PJ, de Marmis RM. Postsynaptic α -adrenoceptors on vascular smooth muscle. *Fed Proc* 1984;43:2923-8.
- Wallin GB, Frisk-Holmberg M. The antihypertensive mechanism of clonidine in man. Evidence against a generalized reduction of sympathetic activity. *Hypertension* 1981;3:340-61.

Pharmacokinetics and Pharmacodynamics of Vecuronium and Pancuronium in Anesthetized Children

Claude Meistelman, MD, Sandor Agoston, MD, PhD, Ursula W. Kersten,
Claude Saint-Maurice, MD, Anton F. Bencini, MD, FFARCS, and Jean-Pierre Loose, MD

MEISTELMAN C, AGOSTON S, KERSTEN UW, SAINT-MAURICE C, BENCINI AF, LOOSE J-P. Pharmacokinetics and pharmacodynamics of vecuronium and pancuronium in anesthetized children. *Anesth Analg* 1986;65:1319-23.

The pharmacokinetics and pharmacodynamics of vecuronium and pancuronium were determined in 12 children (3-6 yr) undergoing minor surgery under 60% nitrous oxide, 1 MAC halothane anesthesia. When the level of anesthesia and the electromyograph (EMG) recording of the adductor pollicis were stable, an intravenous bolus of vecuronium (100 µg/kg) or pancuronium (100 µg/kg) was administered. Plasma concentrations of the two muscle relaxants were determined for 6 hr after the administration by means of a fluorimetric assay followed by a thin layer chromatography. Plasma concentrations of vecuronium and pancuronium declined biexponentially in children and no metabolites could be detected in plasma. The elimination half-lives of vecuronium and pancuronium did not differ significantly. The

volume of distribution at steady state ($V_{d_{ss}}$) was greater ($P < 0.05$) after vecuronium (320 ± 181 ml/kg; mean \pm SD) than after pancuronium (203 ± 36 ml/kg). Plasma clearance of vecuronium (2.8 ± 0.9 ml \cdot min $^{-1}$ \cdot kg $^{-1}$) was greater than that of pancuronium (1.7 ± 0.2 ml \cdot min $^{-1}$ \cdot kg $^{-1}$; $P < 0.05$). Plasma concentrations measured at 10%, 50%, or 90% recovery of the EMG response did not differ significantly for vecuronium and pancuronium. Thus the shorter duration of action of vecuronium is probably due to its greater apparent volume of distribution, as well as to its higher plasma clearance. Thus although the elimination half-lives are comparable, the plasma disappearance of vecuronium is more rapid than that of pancuronium.

Key Words: ANESTHESIA—pediatric. NEUROMUSCULAR RELAXANTS—vecuronium, pancuronium. PHARMACOKINETICS—vecuronium, pancuronium.

In contrast to its quaternary homologue pancuronium, vecuronium has a duration of action and a recovery index that are shorter in both children (1,2) and adults (3,4). Early studies of the pharmacokinetics of vecuronium in children (5) suggested that the short duration of action of vecuronium could be attributed to a short elimination half-life. This conflicted with previous studies in adults (6,7) in which the shorter duration of action of vecuronium was attributed to a more rapid removal from plasma rather than to a shorter elimination half-life when compared to pancuronium. Furthermore, there are few data comparing the disposition of these two drugs after administration of equipotent doses in pediatric surgical patients. To determine whether the differences between vecuronium and pancuronium in children result from changes in

distribution, elimination, or sensitivity, we compared the pharmacokinetics and pharmacodynamics of vecuronium and pancuronium in children during halothane anesthesia.

Methods

Patient Selection and Anesthesia

Twelve children aged between 3 and 6 years (4.4 ± 1.0 yr, mean \pm SD) and undergoing minor genitourinary surgery were studied. None of the children had a disease or received a drug known to alter neuromuscular function. Protocol was approved by the local ethical committee and informed consent was obtained from the parents. Children were numbered consecutively and allocated randomly to receive vecuronium or pancuronium. No premedication was used and anesthesia was induced by halothane and a 60% nitrous oxide-40% oxygen mixture. Once the patient was unconscious an indwelling catheter was inserted into a vein of the forearm. The trachea was intubated without the aid of muscle relaxants and anesthesia

Received from the Department of Anesthesiology, Hôpital Saint Vincent de Paul, Paris, France, and the Institute of Anesthesiology, State University of Groningen, Groningen, The Netherlands. Accepted for publication July 14, 1986.

Address correspondence to Dr. Meistelman, Hôpital Saint Vincent de Paul, 74 avenue Denfert-Rochereau 75674 Paris Cedex 14, France.

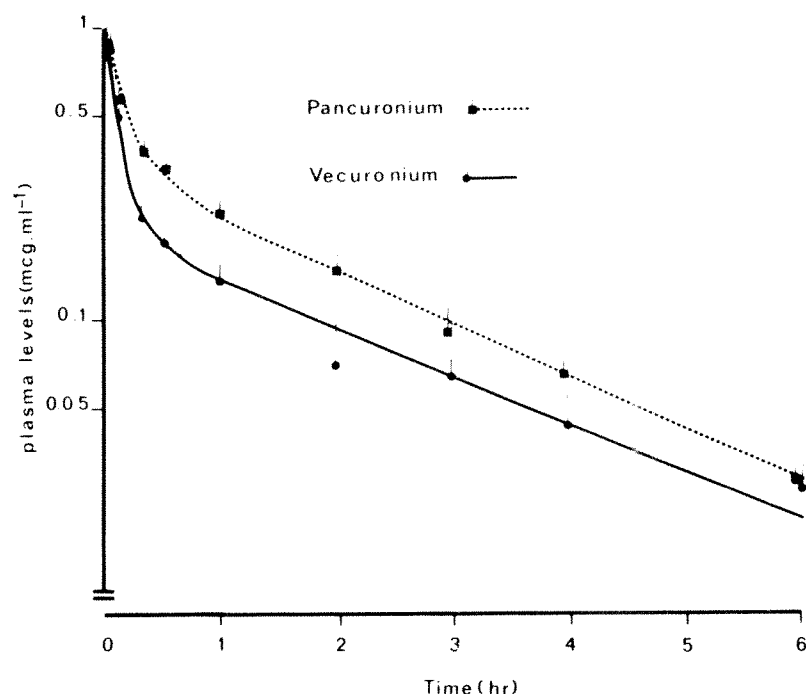


Figure 1. Plasma concentration decay curves following a single bolus (100 μ g/kg) of pancuronium or vecuronium in children.

was maintained with an age-adjusted end-tidal concentration of halothane (1 MAC) and 60% nitrous oxide. Ventilation was controlled to keep end-tidal P_{CO_2} between 30 and 40 mm Hg; body temperature was maintained at 36–37°C.

Clinical Protocol

After induction of anesthesia the ulnar nerve was stimulated at the wrist with single supramaximal 0.2 msec stimuli at 0.1 Hz. The electromyographic response was monitored through electrodes placed over the adductor pollicis. When anesthesia and electromyograph (EMG) recording were stable, an intravenous bolus (10 sec) of vecuronium (100 μ g/kg) or pancuronium (100 μ g/kg) was administered. Blood samples (3 ml) were drawn from the opposite arm 1, 3, 5, 10, 15, 20, 30, 60, 120, 180, 240, and 360 min after the end of the injection. Additional blood samples were drawn at 10%, 50%, and 90% recovery of control value of the EMG response. The concentration of muscle relaxant was defined respectively as Cp10, Cp50, and Cp90.

Chemical Analysis

Blood samples obtained from patients given vecuronium were immediately buffered with 0.75 ml NaH_2PO_4 to prevent the spontaneous hydrolysis of vecuronium that occurs at neutral pH. After centrif-

ugation the plasma samples of all subjects were frozen until analysis. Concentrations of vecuronium and pancuronium in the plasma were measured by a modified fluorimetric assay that was originally described for pancuronium by Kersten et al. (8). This technique has a detection limit of 5 ng/ml for the two drugs and the coefficient of variation is 3–10% in the 5–1000 ng/ml range. Each sample was then further analyzed by thin layer plate chromatography to distinguish vecuronium or pancuronium and their putative metabolites from one another. The density and size of the spots on the plate were compared to those produced by known amounts of the reference compounds. The error of this semiquantitative technique is about 10% and as little as 150 ng of a compound can be detected. None of the drugs used during anesthesia interfered with the assay of vecuronium or pancuronium.

Pharmacokinetic Analysis

Equations of up to five exponential terms were fitted to the plasma concentrations time-data by a computer program using least-squares regression analysis. The choice of the model was determined by F-ratio testing (9). The half-lives of the distribution and the elimination phase, the volume of the central compartment (V_c), the total apparent volume of distribution at steady state (V_{dss}), the volume of distribution β ($V_{d\beta}$) and the plasma clearance (Cl) were calculated using equa-

Table 1. Pharmacokinetic Parameters of Pancuronium in Children, and Vecuronium in Children and Adults

	Age (yr)	$T_{1/2\alpha}$ (min)	$T_{1/2\beta}$ (min)	V_c (ml/kg)	Vd_{ss} (ml/kg)	Clearance (ml·min ⁻¹ ·kg ⁻¹)
Pancuronium	4.5 ± 1.1	5.6 ± 1.4	103 ± 23	74 ± 18	203 ± 36	1.7 ± 0.2
Vecuronium (children)	4.3 ± 0.9	5.3 ± 1.8	123 ± 57	55 ± 22	320 ± 181 ^b	2.8 ± 0.9 ^b
Vecuronium ^a (adults)	20-50	—	117 ± 65	42 ± 25	510 ± 296	3.2 ± 0.2

Values are Mean ± SD.

Abbreviations: $T_{1/2\alpha}$, distribution half-life; $T_{1/2\beta}$, elimination half-life; Vd_{ss} , volume of distribution at steady state; V_c , volume of the central compartment.

^aValues taken from Bencini et al. (6).

^bDifference between vecuronium and pancuronium values is significant, $P < 0.05$.

tion of an intravenous dose of 100 μ g/kg of vecuronium. Absence of putative metabolites of vecuronium the injection until spontaneous recovery of EMG response to 90% of control value), the recovery index (time for the EMG response to recover from 25% to 75% of control value), and the maximum percentage depression of EMG twitch height were measured.

The two-tailed Mann-Whitney U-test was used to evaluate the statistical significance of differences between the two groups; a value of $P < 0.05$ was considered to be significant. All the results are expressed as mean ± SD.

Results

Age and weight did not differ significantly in the two groups. The experimental plasma concentration time-data were best described by a two-compartment model, except for one patient who received pancuronium in whom a three-compartment model was best fitted to the experimental data. No metabolites of pancuronium were found, and none of the three putative metabolites of vecuronium (3-hydroxy, 17-hydroxy, and 3,17-dihydroxy vecuronium) could be detected in plasma, even in the last samples. The plasma concentration decay curves are shown in Figure 1. The plasma concentration curves of vecuronium decreased more rapidly than that of pancuronium. The pharmacokinetics are summarized in Table 1. The distribution half-life ($T_{1/2\alpha}$) and the elimination half-life ($T_{1/2\beta}$) were not significantly different between the two groups.

The total apparent volume of distribution at steady state was greater for vecuronium (320 ± 181 ml/kg) than for pancuronium (203 ± 36 ml/kg, $P < 0.05$). The plasma clearance of vecuronium was 1.6 that of pancuronium ($P < 0.05$). The maximum percentage depression of the electromyographic response was 100% in all the children. The pharmacodynamic parameters and the plasma concentrations during recovery are summarized in Table 2. Plasma concentrations measured at 10%, 50%, and 90% recovery of the

EMG response were slightly lower with vecuronium, but the differences between the two drugs were not significant.

Discussion

The present data demonstrate that, as in adults (3,4), vecuronium has a shorter duration of action and shorter recovery index than pancuronium in children. The plasma concentrations at 10%, 50%, or 90% twitch height recovery were comparable in the two groups, which also means that the potencies of these two muscle relaxants are similar in children.

In this study the fluorimetric assay was used to measure the plasma concentrations of vecuronium and pancuronium. The sensitivity of the fluorimetric assay is actually 5 ng/ml, which is enough to detect these two muscle relaxants for up to 6 hr in plasma after a bolus of 100 μ g/kg. Lack of specificity could be a possible problem for the fluorimetric assay because the deacetylated metabolites are also detected (8). For pancuronium, which is slightly metabolized in humans, the contribution of metabolites to the measured levels is insignificant, as shown by Cronnelly (11). Because the fluorimetric assay measures vecuronium and its deacetylated metabolites, a thin layer chromatography was conducted after the assay to separate and estimate the proportion of metabolites. As in adults, even those with renal failure (6), none of the metabolites could be detected in plasma, even in the last samples. Thus the plasma concentrations of vecuronium are not overestimated after the administration of an intravenous dose of 100 μ g/kg of vecuronium. Absence of putative metabolites of vecuronium in plasma could be surprising, but can be explained by the predominant hepatic uptake and elimination of vecuronium. Metabolites of vecuronium are probably eliminated by biliary excretion and thus do not appear in plasma.

In children the most important difference between vecuronium and pancuronium is the greater apparent

Table 2. Pharmacodynamic Parameters and Plasma Concentrations during Recovery.

	Percentage of depression (%)	Duration of action (min)	Recovery index (min)	Cp 10 ($\mu\text{g/ml}$)	Cp 50 ($\mu\text{g/ml}$)	Cp 90 ($\mu\text{g/ml}$)
Pancuronium	100	92 \pm 9	28 \pm 6	0.33 \pm 0.05	0.24 \pm 0.04	0.18 \pm 0.02
Vecuronium	100	34 \pm 4 ^a	7 \pm 2 ^a	0.25 \pm 0.10	0.21 \pm 0.05	0.14 \pm 0.06

All values are Mean \pm SD.

Abbreviations: Cp 10, Cp 50, Cp 90, concentration of muscle relaxant at, respectively, 10%, 50%, and 90% of recovery to control value of electromyograph response.

^aVecuronium and pancuronium values differ significantly.

volume of distribution at steady state of vecuronium. This finding, already observed in adults (7,12), could be due to the relative lipophilicity of vecuronium compared with pancuronium, and possibly to the higher liver uptake of vecuronium. The liver probably represents an important fraction of the volume of distribution of vecuronium (12). The higher plasma clearance of vecuronium could be due to this extensive uptake by the liver followed by biliary excretion; at least 10–30% of a dose of vecuronium is eliminated as both unchanged drug and metabolites in the bile in humans (12). Because halothane decreases hepatic blood flow (13) and so decreases hepatic elimination, the alveolar concentration of halothane was maintained within a narrow range in all the children to minimize this variable.

The elimination half-life of vecuronium in children in the present study was close to the values reported in our previous studies in adults (6) with the same dose and the same type of anesthesia (nitrous oxide–halothane). This value is longer than that obtained in early kinetic studies in man (14), studies that suffered from a relatively insensitive assay (high performance liquid chromatography) (15). Because of this insensitivity, a long plasma concentration decay curve could not be obtained, which led to the calculation of an erroneously rapid decay of the plasma concentrations of vecuronium, which in turn led to the calculation of an elimination half-life value that was too brief. Recently Fisher et al., (5) using a sensitive and specific mass spectrometry, reported an elimination half-life of 41 min in children. However, duration of sampling was shorter than in our study and could have underestimated the terminal half-life. Furthermore the authors did not mention whether they buffered plasma samples to prevent in vitro degradation of vecuronium, which is known to occur to a substantial degree when plasma pH is above 4 (7). Pharmacokinetic parameters of pancuronium in children are comparable to values reported in adults (11,16). The plasma clearance of pancuronium does not seem to change with age, probably because pancuronium

is largely eliminated by the kidney and the renal function is the same in children and adults.

The shorter duration of action of vecuronium is due to the more rapid removal of vecuronium from the plasma, which is in turn probably due to the greater apparent volume of distribution. Even if the elimination half-life of these two muscle relaxants is comparable and if the plasma concentration decay curves are almost the same during the elimination phase in children, the disappearance of pancuronium from plasma is delayed because of differences during the distribution phase. The threshold concentrations below which no pharmacologic effects are to be expected are therefore reached sooner with vecuronium (at the end of the distribution phase). As shown in Figure 1, the plasma concentrations of vecuronium are under the threshold level 30–40 min after the administration. This finding agrees with the duration of action seen in this and other studies (1,17). In contrast to vecuronium, the plasma concentrations of pancuronium are still above the pharmacologically active levels for a considerable length of time.

In summary, in children under halothane anesthesia the differences in duration of action of vecuronium and pancuronium could be explained by pharmacokinetic mechanisms. At a dose of 100 $\mu\text{g/kg}$ the duration of action of vecuronium appears to be governed by the distribution phase whereas the duration of action of pancuronium is governed by the elimination phase.

References

1. Goudsouzian NG, Martyn JAJ, Liu LMP, Gionfriddo M. Safety and efficacy of vecuronium in adolescents and children. *Anesth Analg* 1983;62:1083–8.
2. Fisher DM, Miller RD. Neuromuscular effects of vecuronium (Org. NC 45) in infants and children during N_2O , halothane anesthesia. *Anesthesiology* 1983;58:519–23.
3. Agoston S, Salt P, Newton DEF, Bencini A, Boosma P, Erdmann W. The neuromuscular blocking action of Org NC 45, a new pancuronium derivative in anaesthetized patients. *Br J Anaesth* 1980;52:53S–8S.

4. Fahey MR, Morris RB, Miller RD, Sohn YJ, Cronnelly R, Gencarelli P. Clinical pharmacology of Org NC 45: a new non-depolarizing muscle relaxant. *Anesthesiology* 1981;55:6-11.
5. Fisher DM, Castagnoli K, Miller RD. Vecuronium kinetics and dynamics in anesthetized infants and children. *Clin Pharmacol Ther* 1985;37:402-6.
6. Bencini AF, Scaf AHJ, Sohn YJ, Meistelman C, Lienhart A, Kersten UW, Schwarz S, Agoston S. Disposition and urinary excretion of vecuronium bromide in anesthetized patients with normal renal function and renal failure. *Anesth Analg* 1986;65:245-51.
7. Sohn YJ, Bencini AF, Scaf AHJ, Kersten UW, Agoston S. Comparative pharmacokinetics and dynamics of vecuronium and pancuronium in anesthetized patients. *Anesth Analg* 1986; 65:233-9.
8. Kersten UW, Meijer DKF, Agoston S. Fluorimetric and chromatographic determination of pancuronium bromide and its metabolites in biological materials. *Clin Chim Acta* 1973; 44:59-66.
9. Boxenbaum G, Riegelman S, Elashoff RM. Statistical estimations in pharmacokinetics. *J Pharmacokinet Biopharm* 1974;2:123-48.
10. Gibaldi M, Perrier D. Multicompartment models. In: Gibaldi M, Perrier D, eds. *Pharmacokinetics*. New York: Marcel Dekker, 1975:45-89.
11. Cronnelly R, Fisher DM, Miller RD, Gencarelli P, N'Guyen Gruenke L, Castagnoli JN. Pharmacokinetics and pharmacodynamics of vecuronium (Org NC 45) and pancuronium in anesthetized humans. *Anesthesiology* 1983;58:404-8.
12. Bencini A, Scaf AHJ, Sohn YJ, Kersten UW, Agoston S. Clinical pharmacokinetics of vecuronium. In: Agoston S, Bowman WC, Miller RD, Vibi-Mogensen J, eds. *Clinical experiences with Norcuron*. Amsterdam: Excerpta Medica 1983:115-23.
13. Gelman SI. Disturbances in hepatic blood flow during anesthesia and surgery. *Arch Surg* 1976; 111:881-3.
14. Van Der Veen F, Bencini A. Pharmacokinetics and pharmacodynamics of Org NC 45 in man. *Br J Anaesth* 1980;52:375-415.
15. Paanakker JE, Van De Laar GLM. Determination of Org NC 45 (a myoneural blocking agent) in human plasma using high performance normal phase liquid chromatography. *J Chromatography* 1980;183:459-69.
16. Duvaldestin P, Saada J, Berger JL, D'Hollander A, Desmont JM. Pharmacokinetics, pharmacodynamics and dose response relationships of pancuronium in control and elderly subjects. *Anesthesiology* 1982;56:36-40.
17. Meistelman C, Loose JP, Saint-Maurice C, Delleur MM, De Silva GL. Clinical pharmacology of vecuronium in children during nitrous oxide-oxygen-halothane anaesthesia. *Br J Anaesth*. 1986;58:996-1000.

Retrobulbar Anesthesia: The Role of Hyaluronidase

J. Martin V. Nicoll, FFASA, Beatrix Treuren, FFARCS, P. Arun Acharya, FFARCS,
Kjell Ahlen, MD, and Michael James, FFARCS

NICOLL JMV, TREUREN B, ACHARYA PA, AHLEN K, JAMES M. Retrobulbar anesthesia: the role of hyaluronidase. *Anesth Analg* 1986;65:1324-8.

The present study was conducted in 100 patients receiving retrobulbar block for ophthalmic surgery to compare the efficacy of local anesthetic solutions with and without hyaluronidase. All patients received 3.5 ml of a mixture of 3 ml of 0.5% bupivacaine and 2 ml of 2% lidocaine. Seventy-

five international units of hyaluronidase were diluted in 5 ml of the local anesthetic mixture and used for 50 of the blocks. The remainder did not receive hyaluronidase. A consistently better motor blockade was achieved with hyaluronidase ($P < 0.001$ at 10, 15, and 20 min). This finding has not been conclusively demonstrated before.

Key Words: ANESTHESIA—ophthalmologic. ANESTHETIC TECHNIQUES, REGIONAL—retrobulbar.

Until recently retrobulbar anesthesia for ophthalmic surgery was administered almost exclusively by the ophthalmologist, and only rarely did the anesthesiologist perform the block. On starting a new anesthesia service it was necessary to reexamine and test the validity of old methods. Retrobulbar block was first described in 1914 by Pooley who used a mixture of procaine and epinephrine (1). Since that time several improvements have been instituted. Based on the chance finding that an aqueous testicular extract (2), later identified as hyaluronidase (3), enhanced the spread of vaccinia virus, Atkinson added 30 turbidity reducing units of hyaluronidase to 5 ml of 2% procaine hydrochloride with 0.4% potassium chloride and one drop of epinephrine (1:1000). He hoped that the hyaluronidase would help to spread the local anesthetic. From his experience with 109 cases reported in 1949 (4), he concluded that when using this combination of agents, a more effective akinesia of the orbicularis and extraocular muscles was obtained. There was no control group in his study and the results were subjective.

Hyaluronidase depolymerizes hyaluronic acid, which is now regarded as the tissue cement or ground substance of the mesenchyme aiding the local spread

of the anesthetic agent (5). Although it is the author's impression that most ophthalmologists use hyaluronidase today, anesthesiologists rarely use it as an adjunct to local anesthesia because improved efficacy of neural blockade has not been demonstrated elsewhere in the body (6-8). The addition of hyaluronidase to mepivacaine has been reported to produce a more rapid onset without overall improvement in the retrobulbar block (9). With the improved spreading power of newer local anesthetic agents the necessity for its continued use has been questioned (10). This present study was designed to compare the efficacy of retrobulbar blockade with or without hyaluronidase.

Methods

The protocol was approved by the hospital research committee. One hundred consecutive patients scheduled for anterior segment surgery under local anesthesia were randomly divided into two groups, A and B. All patients were in ASA categories 1-3, but patients with only one eye, and those for whom the Honan intraocular pressure reducer (11,12) had not been prescribed, were excluded. The Honan intraocular pressure reducer is a pneumatic balloon that can be inflated to apply an evenly distributed pressure over the eye (Fig. 1). Facial nerve blocks were performed in all cases using an extraorbital technique. An attendant nurse anesthetist monitored vital signs throughout the procedure.

Coded 5 ml syringes filled immediately before in-

Received from the Department of Anesthesia, King Khaled Eye Specialist Hospital, Riyadh, Saudi Arabia. Accepted for publication June 6, 1986.

Address correspondence to Dr. Nicoll, Department of Anesthesia, King Khaled Eye Specialist Hospital, Riyadh 11462, Saudi Arabia.

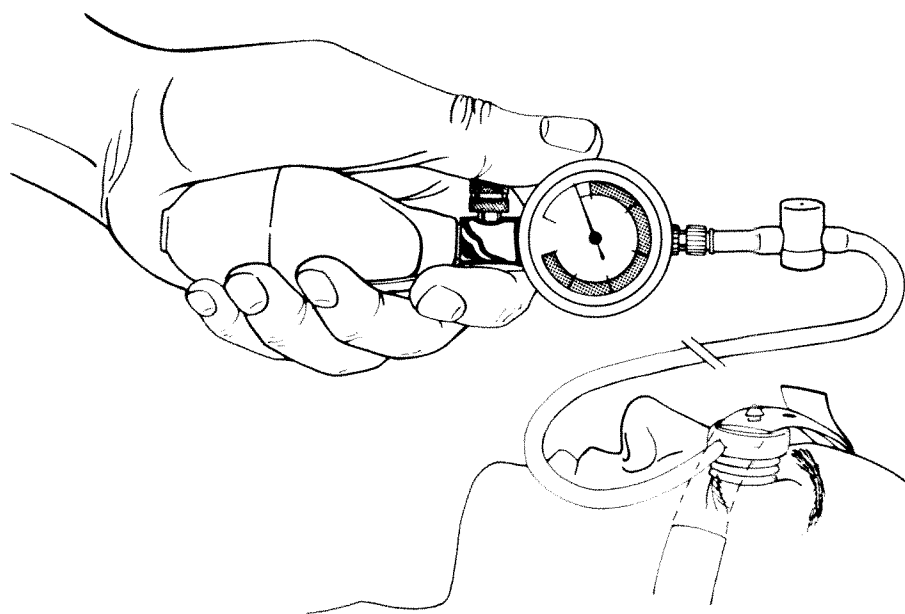


Figure 1. After the retrobulbar block had been given, a Honan Balloon was applied to the orbit and inflated to 35 mm Hg.

jection by the nurse according to a random selection contained either 3 ml bupivacaine, 0.5% plus 2 ml lidocaine (group A), or 3 ml bupivacaine, 0.5%, plus 2 ml lidocaine, 2%, plus hyaluronidase, 75 IU (group B). The contents of the syringes were not known by the anesthesiologists.

Five different anesthesiologists used a standard technique for retrobulbar block. The patient was instructed to look superonasally. Using a percutaneous inferotemporal approach, a 35 mm 25-gauge needle was aimed to penetrate the muscle cone between the lateral and inferior rectus muscles, through which 3.5 ml of the local anesthetic was injected. The eyelids were then taped closed, and a gauze swab was placed over the closed eyelids. A Honan balloon (Fig. 1) was applied to the orbit and inflated to a pressure of 35 mm Hg. It was then removed at 10-min intervals for assessment of akinesia of the globe. Orbital anatomy and degree of patient cooperation were scored for each patient immediately after the injection (0, easy; 1, average; 2, difficult anatomy; 0, good cooperation; 1, average cooperation; 2, poor cooperation).

The anesthesiologist who performed the block assessed the results of the local anesthetic for akinesia of the globe at 10, 20, and 30 min after injection. A scoring system from 0-2 was used to assess the movements in the four quadrants: 0, no block; 1, partial block; and 2, complete block of the associated rectus muscle. Complete akinesia in all four quadrants gave an akinesia score of 8 (Fig. 2). Once complete akinesia had been achieved as compared to the other eye, no further assessment was made. Additional local an-

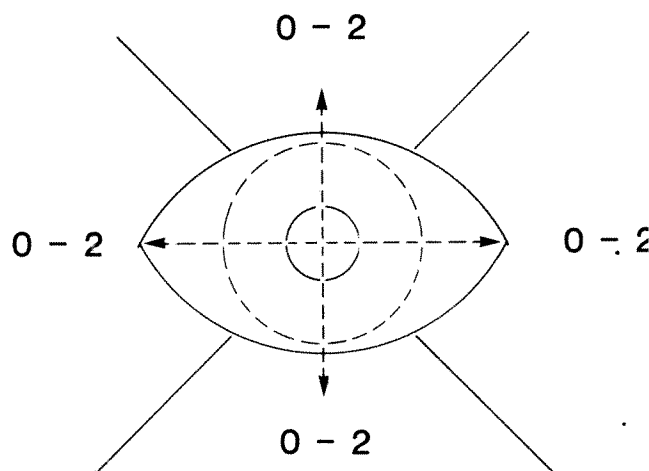


Figure 2. Scoring method for akinesia of the globe: 0, full movement of the associated rectus muscle; 1, partial movement of the associated rectus muscle; 2, complete paralysis of associated rectus muscle.

esthetic was injected after 30 min if the initial block had not been sufficiently successful to allow surgery to proceed comfortably.

The χ^2 test was used to compare the results obtained in the two groups. The level of statistical significance was chosen as $P < 0.001$.

Results

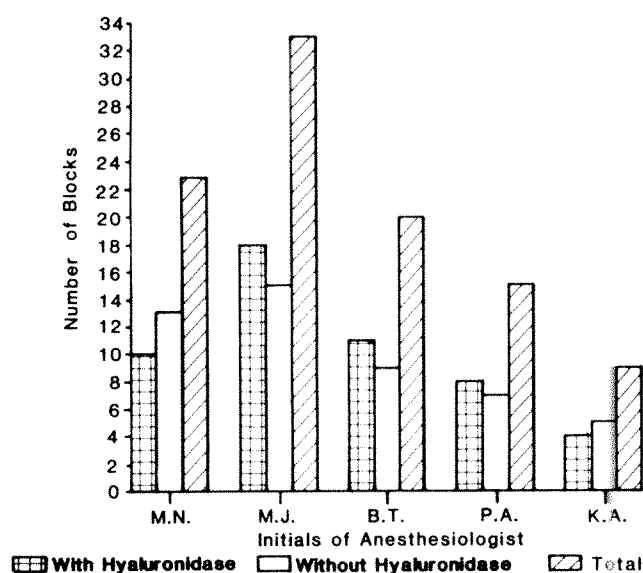
Table 1 shows that the mean ages, sex, eye, difficulty of the anatomy, degree of patient cooperation, and

Table 1. Distribution of Patients in the Hyaluronidase and Non-hyaluronidase Groups

	Average age ^a (yr)	Sex (M/F)	Eye side (R/L)	Block to end surgery time ^a (min)	Patient cooperation score ^b			Anatomy score ^c		
					0	1	2	0	1	2
With hyaluronidase	58 ± 11	36/14	27/23	93 ± 29	12	33	5	9	38	3
Without hyaluronidase	62 ± 11	40/10	26/24	106 ± 22	14	31	5	6	39	5

^aMean ± SD.

^bPatient cooperation score: 0, good; 1, average; 2, poor.

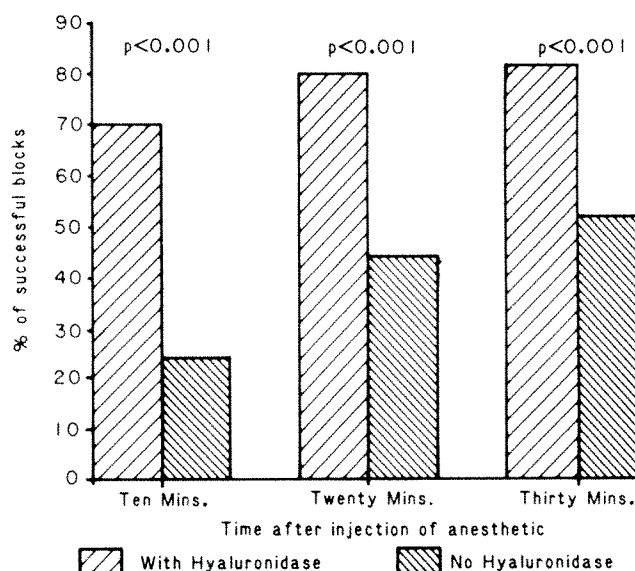
^cAnatomy score: 0, easy; 1, average; 2, difficult.

Figure 3. Distribution of retrobulbar blocks performed by each anesthesiologist on group A and B patients was not significantly different ($P > 0.5$).

duration of surgery were matched in the two groups. Each anesthesiologist gave a similar number of blocks to both group A and group B patients (Fig. 3).

There was a significantly greater number of blocks achieving complete akinesia (akinesia score greater than 7) with hyaluronidase than without hyaluronidase (Fig. 4). The difference was most marked at 10 min, but was still significant at 20 and 30 min after injection. Surgically acceptable anesthesia was sometimes achieved when residual movement remained in one muscle (akinesia score greater than 6). When including these patients in the results, the results in the hyaluronidase group were still significantly better at 10 min, although this difference was not significant at 20 and 30 min after the block (Fig. 5).

Discussion

The improved efficacy of retrobulbar block by the addition of hyaluronidase to the local anesthetics was


Figure 4. The frequency with which a single retrobulbar injection of local anesthetic gave complete akinesia of the globe (akinesia score >7) with and without the addition of hyaluronidase. Significantly better results are shown with hyaluronidase at all times (10, 20, and 30 min after injection $P < 0.001$).

clearly demonstrated by the trial. This difference was soon apparent to the nursing staff who had coded the syringes, but their impression was not communicated to the anesthesiologists until 100 blocks had been performed. Originally the authors were skeptical that any difference at all would be demonstrated, and a far larger trial had been contemplated. However, on completion of this number it was clear that to continue to perform retrobulbar block without the addition of hyaluronidase would be unjustified. That hyaluronidase has not been shown to improve the efficacy of local anesthetics administered in other types of nerve blocks (6-8) may be accounted for by the fact that the bony walls of the orbit and the application of the pressure balloon prevent the further dispersal of the anesthetic, thus confining the spreading action of the hyaluronidase to the intraorbital structures. It has been suggested that the mechanical force of increased interstitial pressure either markedly accelerates or is a prerequisite for hyaluronidase activity (13).

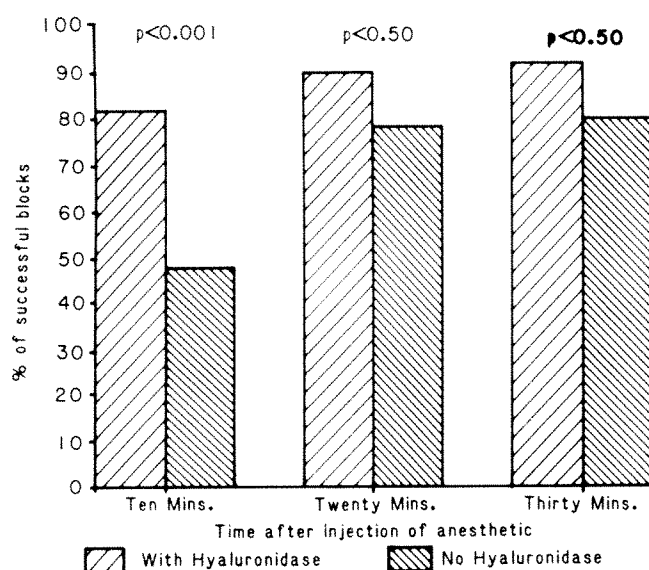


Figure 5. The incidence of complete block or partial residual movement in one muscle after single retrobulbar injection of anesthetic (akinesia score >6). At 10 min the results in the hyaluronidase group were significantly better ($P < 0.001$), but at 20 and 30 min after injection the difference was not significant ($0.50 > P > 0.10$).

There are few contraindications to the use of hyaluronidase. A study linking the incidence of aphakic cystoid macular edema to hyaluronidase (14) was later refuted (15). Rare instances of allergy have been reported (16), although in the author's experience of more than 6000 hyaluronidase administrations, allergy has not been seen. It might be argued that the incidence of central spread of the anesthetic could be enhanced by the addition of hyaluronidase, but with a low overall instance of this complication, it would be difficult to prove. Similarly, an increased rate of vascular absorption and subsequent toxicity was not likely to appear in the hyaluronidase group, as the overall dosage of marcaine in the smallest adult (weight 40 kg) was only a fraction of the recommended maximum dose (2 mg/kg body weight) (17). No complications relating to central spread or systemic toxicity were seen in this trial.

The study also confirmed previous findings (4,9) that anesthetic solutions containing hyaluronidase provide a more rapid onset of anesthesia. More important was the fact that the duration of nerve block in both groups was sufficient to complete the surgery (Table 1). There was no need to expose the patient to the additional risk of epinephrine for the purpose of extending the duration of the block. For practical reasons the exact duration of the anesthesia in the two groups could not be measured, but a mean time of

± 100 min elapsed between the retrobulbar injection and the end of surgery. Planned intraocular surgery of much longer time than this is not practical because patients can become restless.

Each time an injection has to be made behind the eyeball, there is a small risk of complications, whether they be hemorrhage, puncture of the globe, optic nerve damage, central spread, or anesthetic toxicity. Successful blockade from a single injection is therefore desirable, and our study showed that this is most likely to be achieved when hyaluronidase is added to the local anesthetic solution. Accurate placement of local anesthetic within the muscle cone should give a uniformly good block. However, such placement is not always possible, and there is some evidence that it may not even be advisable (18). The additional spreading action that the hyaluronidase gives to the local anesthetic is particularly important when the injection is not made within the cone but in the tissue surrounding it. This finding might have useful clinical application for other local anesthetic injections in enclosed spaces, such as digital ring block under tourniquet

References

1. Pooley GH. An improvement in local anaesthesia in operation upon the eye. *The Ophthalmoscope* 1914;12:464-7.
2. Duran Reynals F. The effect of extracts of certain organs from normal and immunized animals on the infecting power of the vaccine virus. *J Exp Med* 1929;50:327-39.
3. Chain E, Duthie ES. Identity of hyaluronidase and spreading factor. *Br J Exp Pathol* 1940;21:324-38.
4. Atkinson WS. Use of hyaluronidase with local anesthesia in ophthalmology: preliminary report. *Arch Ophthalmol* 1949;42:628-33.
5. Vickers MD, Schnieden H, Wood-Smith FG. *Drugs in anaesthetic practice*. 6th ed. London: Butterworths 1984:423.
6. Scott DB. Hyaluronidase in epidural analgesia. *Br J Anaesth* 1956;28:187-92.
7. Payne JN, Rupp NH. The use of hyaluronidase in caudal block anaesthesia. *Anesthesiology* 1951;12:164-72.
8. Eckenhoff JE, Kirby CK. The use of hyaluronidase in regional nerve blocks. *Anesthesiology* 1951;12:27-32.
9. Mindel JS. Value of hyaluronidase in ocular surgical akinesia. *Am J Ophthalmol* 1978;85:643-6.
10. Scott DB, Cousins MJ. Clinical pharmacology of local anesthetic agents. In: Cousins MJ, Bridenbaugh PO, eds. *Neural blockade in clinical anesthesia and management of pain*. JB Lippincott 1980:103-4.
11. Martin NF, Stark WJ, Maumenee AE, Bruner WE, Rosenbaum P. Use of the Honan intraocular pressure reducer at the Wilms Institute. *Ophthalmic Surg* 1982;13:101-3.
12. Jay WM, Carter H, Williams B, Green K. Effect of applying the Honan intraocular pressure reducer before cataract surgery. *Am J Ophthalmol* 1985;100:523-7.

13. Lebensohn JE. Hyaluronidase in ocular surgery and therapy. *Am J Ophthalmol* 1950;33:865-70.
14. Roper DL, Nisbet RM. Effect of hyaluronidase on the incidence of cystoid macular edema. *Ann Ophthalmol* 1978;10:1673-8.
15. Kraff MC, Sanders DR, Jampol LM, Lieberman HL. Effect of retrobulbar hyaluronidase on pseudophakic cystoid macular edema. *An Intra-ocular Implant Soc J* 1983;9:184-5.
16. Taylor IS, Pollowitz JA. Case report (letter). *Ophthalmology* 1984;91:1003.
17. Atkinson RS, Rushman GB, Alfred Lee J. A synopsis of anesthesia 9th ed. Bristol: Wright. PSG, 1982:662.
18. Davis II DB, Mandel MR. Posterior peribulbar anesthesia: an alternative to retrobulbar anesthesia. *J Cataract Refract Surg* 1986;12:182-5.

Changes in Heart Rate and Rhythm after Intramuscular Succinylcholine with or without Atropine in Anesthetized Children

Raafat S. Hannallah, MD, Tae H. Oh, MD, Willis A. McGill, MD, and Burton S. Epstein, MD

HANNALLAH RS, OH TH, MCGILL WA, EPSTEIN BS.
Changes in heart rate and rhythm after intramuscular succinylcholine with or without atropine in anesthetized children. *Anesth Analg* 1986;65:1329-32.

The effects of intramuscular injections of succinylcholine with or without atropine on heart rate and rhythm were studied in 50 unpremedicated children 6-18 months of age. All had anesthesia induced with N₂O-O₂ and halothane 2% by face mask. Sixty seconds later, one of four study drugs or drug combinations was injected into the deltoid muscle of patients in groups 1-4. Following injection, halothane concentration was reduced to 1%, and ventilation was controlled. Patients given atropine only (0.02 mg/kg), succinylcholine only (4 mg/kg), or a combination of both (4 mg/kg succinylcholine plus 0.02 mg/kg atropine) showed transient increases in heart rate to $106 \pm 7.5\%$, $113 \pm 11.8\%$, and $109 \pm 10.1\%$ (mean \pm SD) of control, followed by a decrease to $78 \pm 6.7\%$, $79 \pm 9.4\%$, and $80 \pm 10.5\%$, respectively, in 2-3 min after injection. Patients given a

combination of succinylcholine (4 mg/kg) plus a higher dose of atropine (0.03 mg/kg) also had a transient increase in heart rate to $107 \pm 7.5\%$, followed by a decrease to $82 \pm 11.8\%$ 2 min after injection. However, this group differed from the other three groups in presenting a second, prolonged increase in heart rate to $115 \pm 9.0\%$ of preinjection levels. Patients in group 5 (controls) received no injections. Their heart rate decreased to $76 \pm 10.78\%$ of preinduction level within 90 sec of induction, and remained unchanged thereafter. We conclude that succinylcholine (4 mg/kg) can be used intramuscularly with or without atropine (0.02 mg/kg) in lightly anesthetized young children without producing severe bradycardia. If an increase in heart rate is desired, a higher dose of atropine (0.03 mg/kg) is recommended.

Key Words: ANESTHESIA—pediatric. NEUROMUSCULAR BLOCKING AGENTS, SUCCINYLCHOLINE—intramuscular.

Sinus bradycardia after intravenous injection of a second dose of succinylcholine is a well recognized phenomenon (1). It is also known that in infants and young children arrhythmias including bradycardia, nodal rhythm, and ventricular ectopic beats are commonly seen following a single intravenous injection of succinylcholine (2). The use of intravenous atropine (0.01-0.02 mg/kg) immediately before or combined with succinylcholine is effective in preventing bradycardia and, therefore, is widely recommended (3).

Following intramuscular injection of succinylcholine, however, bradycardia is believed to be either absent or less profound than following intravenous administration (2). Thus, some investigators question

the need to administer atropine when succinylcholine is injected intramuscularly. Others have suggested that the simultaneous intramuscular injection of succinylcholine and atropine should be avoided (3) because the initial vagotonic action of atropine administered intramuscularly may predominate (4). If the transient vagotonic effect of atropine were to coincide with that of succinylcholine, the effects may be additive and result in profound bradycardia. Whether or not these potential drug interactions have such an adverse effect on heart rate in a clinical setting has not been objectively documented.

The purpose of this study was to evaluate the effects of intramuscular injections of atropine and succinylcholine, alone and in various combinations, on heart rate and rhythm in young children following induction of anesthesia with N₂O-O₂ and halothane

This work was presented in part at the Annual Meeting of the American Society of Anesthesiologists, Atlanta, Georgia, October 1983.

Received from the Departments of Anesthesiology and Child Health and Development, Children's Hospital National Medical Center and George Washington University, Washington, D.C. Dr. Oh is currently at Yale University School of Medicine, New Haven, Connecticut. Accepted for publication June 26, 1986.

Address correspondence to Dr. Hannallah, Department of Anesthesiology, Children's Hospital National Medical Center, Washington, DC 20010.

Methods

Fifty children aged 6-18 months scheduled for elective surgical procedures requiring general endotracheal anesthesia were studied. The study was approved by the institutional review board, and parents

consents were obtained. All patients were ASA I; none received preoperative medication. The first 40 patients were randomly assigned to one of four groups (Table 1). In all cases, anesthesia was induced with the infant spontaneously breathing a mixture of N_2O-O_2 and 2% halothane. Sixty seconds after the start of induction, one of four study drugs or drug combinations was injected into the deltoid muscle. When the injection included succinylcholine, the dose was calculated based on the current recommendation in the literature (5). Following the injection, the inspired halothane concentration was reduced to 1%, with ventilation assisted and then controlled for 5 min at which time the study was completed (Fig. 1). Patients who received succinylcholine (with or without atropine) were then intubated, and those who received atropine only had intravenous succinylcholine injected prior to endotracheal intubation. The remaining 10 patients (group 5) received the same halothane concentration with no injections, and served as controls. Additional atropine was always available during the study should the heart rate drop to 60 beats/min or less.

A lead II ECG was continuously monitored and recorded from the start of anesthesia induction until 1 min following intubation. Heart rate signals from the monitor were connected to a multimeter/calculator (Calcumeter 4100, Electro Scientific Industries, Portland, OR) programed to convert voltage output from the monitor to a digital display of heart rate. The signals were sampled, and the mean heart rate was displayed, stored, and printed by the system every 5 sec. Changes in heart rate from preinjection levels were computed for each patient, and the minimal decrease and maximal increase in heart rate in each group was recorded. Blood pressure was recorded before induction, and every 60 sec thereafter using a Dinamap vital signs monitor (Critikon, Tampa, FL), and the printed ECG strip was visually scanned for detection of dysrhythmias. Patients in groups 1-4 were compared for changes in heart rate and blood pressure following drug injection by analysis of variance. Because patients in groups 1 and 5 were not anesthetized and/or relaxed enough for endotracheal intubation at the end of 5 min, no comparison was made of the changes in heart rate and blood pressure associated with endotracheal intubation among the five groups.

Results

The five patient groups were not significantly different in age, body weight, or preoperative fasting period. The minimal and maximal changes in heart rate

Table 1. Dosage of Succinylcholine and/or Atropine

Group (n = 50)	Succinylcholine (mg/kg)	Atropine (mg/kg)
1	none	0.02
2	4	none
3	4	0.02
4	4	0.03
5	none	none

(expressed as a percentage from preinjection control levels) were plotted against time for patients in groups 1-4 (Fig. 2). The pattern of change in heart rate was similar in groups 1, 2, and 3. The heart rate showed an early transient increase within the first 1.5 min following injection to a maximum of (mean \pm SD) $106 \pm 7.5\%$, $113 \pm 11.8\%$, and $109 \pm 10.1\%$ relative to the preinjection level for groups 1, 2, and 3, decreased to a minimum of $78 \pm 6.7\%$, $79 \pm 9.4\%$, and $80 \pm 10.5\%$, respectively, between 2 and 3 min, and remained unchanged thereafter. The differences between the three groups were not statistically significant ($P > 0.05$).

Patients in group 4 showed a different pattern. Following a transient increase in heart rate associated with the intramuscular injection to $107 \pm 7.6\%$ of the preinjection level, the heart rate decreased to $82 \pm 11.8\%$ of control in 131 sec, increased to $115 \pm 9.0\%$ in 208 sec, and remained at the level throughout the study period. This maximum increase in heart rate and the difference in heart rate at the end of the final 3 min for group 4 was statistically significant ($P < 0.05$) from the other three groups. In the control patients (group 5), the heart rate decreased to $76 \pm 10.8\%$ of preinduction level within 90 sec of anesthesia induction, and remained unchanged thereafter.

No serious dysrhythmias were present in any of the patients during the study period. One patient in group 2, however, developed a sinus bradycardia (66 beats/min) during laryngoscopy. Two brief episodes of nodal rhythm were recorded, one in each of groups 3 and 4. All resolved spontaneously following tracheal intubation. Changes in systolic blood pressure from preinduction values were not significantly different among the groups (Table 2).

Discussion

Bradycardia and cardiac arrhythmias after the intravenous administration of succinylcholine in infants and children are believed to be related to stimulation of cholinergic autonomic receptors. These include nicotinic receptors in both sympathetic and parasympathetic ganglia and muscarinic receptors in the sinus

Figure 1. Sequence of study events from induction to endotracheal intubation. Statistical analysis was performed on data collected from time zero [injection], through 300 sec [just prior to tracheal intubation].

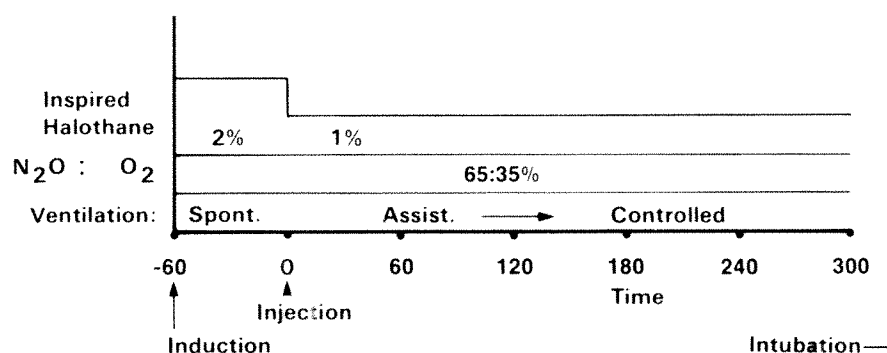


Figure 2. Changes in heart rate in groups 1-4 after drug injection at time zero. The maximum increase in heart rate, and the heart rate at the end of the study period (300 sec) prior to the tracheal intubation was significantly higher in group 4, compared with groups 1, 2, and 3 ($P < 0.05$).

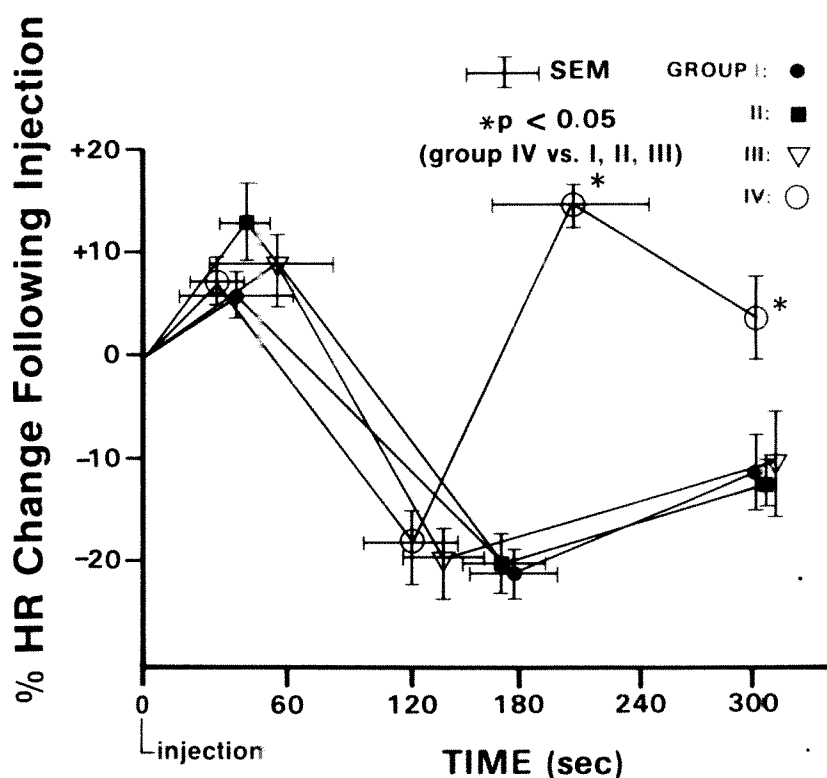


Table 2. Systolic Blood Pressure Values in mm Hg

Group (n = 50)	1	2	3	4	5
On admission	84.2 (5.45)	85.9 (6.71)	85.5 (8.81)	90.7 (13.35)	87.7 (7.81)
Before induction	98.6 (18.82)	96.1 (20.38)	102.0 (16.71)	102.0 (25.73)	96.8 (19.35)
Before intubation	106.5 (24.65)	104.8 (16.94)	111.9 (16.10)	120.1 (19.38)	93.6 (26.18)

Mean \pm SD.

(S-A) node of the heart. Sinus bradycardia results from stimulation of the cardiac muscarinic receptors in the S-A node. If the resultant bradycardia is slower than the existing sinus rate, junctional or nodal rhythm

occurs. This is frequently evident in adults when second dose of intravenous succinylcholine is given shortly after the first, or in children after a single dose of intravenous succinylcholine.

Intramuscular injection of succinylcholine is a common practice in anesthesia for infants and young children (3). The technique provides excellent conditions for tracheal intubation without the depression of cardiovascular function that may occur when halothane or other potent inhalational agents are used to produce the degree of muscle relaxation required for direct laryngoscopy and tracheal intubation. Intramuscular succinylcholine is easily administered even by an anesthesiologist working alone before an intravenous route can be secured; and many of the possible adverse effects associated with intravenous succinylcholine are believed to be avoided (2).

This study confirms that succinylcholine can be injected intramuscularly in lightly anesthetized infants (1% inspired halothane) without producing severe bradycardia. Adding atropine (0.02 mg/kg) did not result in excessive slowing of the heart rate as was previously feared (3). The heart rate remained below control values; however, if an increase in heart rate

is considered desirable prior to tracheal intubation, a higher dose of atropine (0.03 mg/kg) is recommended.

The authors thank Urs E. Ruttimann, PhD, for performing the statistical analysis in this study.

References

1. Lupprian KG, Churchill-Davidson HC. Effect of suxamethonium on cardiac rhythm. *Br Med J* 1960;4:1774-7.
2. Craythorne NWB, Turndorf H, Dripps RD. Changes in pulse rate and rhythm associated with the use of succinylcholine in anesthetized children. *Anesthesiology* 1960;21:465-70.
3. Smith RM. Use of muscle relaxants. In: *Anesthesia for infants and children*, 4th ed. St. Louis: The CV Mosby Company, 1980;255-6.
4. Chamberlain DA. Effects of atropine on heart rate in healthy man. *Lancet* 1976;2:12-5.
5. Liu LMP, DeCook TH, Goudsouzian NG, et al. Dose response to intramuscular succinylcholine in children. *Anesthesiology* 1981;55:599-602.

Pulse Oximetry and Circulatory Kinetics Associated with Pulse Volume Amplitude Measured by Photoelectric Plethysmography

Jong-Min Kim, MD, Kasumi Arakawa, MD, PhD, Kirk T. Benson, MD, and
Deanna K. Fox, MD

KIM J-M, ARAKAWA K, BENSON KT, FOX DK. Pulse oximetry and circulatory kinetics associated with pulse volume amplitude measured by photoelectric plethysmography. *Anesth Analg* 1986;65:1333-9.

Through a catheter placed in a superficial vein on the finger, we observed a pulsatile venous pressure. To delineate the relationship between the pulsatile venous pressure and the pulse volume amplitude (PVA) recorded by photoelectric plethysmography (PEPG), both tracings were simultaneously recorded. When the PVA changed acutely or gradually, the venous pulse pressure and mean venous pressure simultaneously followed the same trend. We also found that mean PvO_2 (135 mm Hg) was greater when the PVA and venous pulse pressure increased above the level (50 mm Hg) observed when they decreased. These findings suggested that the finger pulse detected by PEPG, as well as by pulse oximetry, is caused by pulsations in veins rather than by pulsations in arterial beds. In experiments to evaluate the

validity of this hypothesis, we found that the average value of hemoglobin saturation ($\%SaO_2$) measured by the pulse oximeter of the dependent fingertip and finger base when dependent was 1.5% and 7.8% lower than when the fingertip and finger base were elevated. Also, the PVA detected by the pulse oximeter followed the same trend as $\%SaO_2$. This finding was explained by venous congestion in the dependent finger. On the basis of the high venous pressure, the behavioral trends between the PVA and venous pressure, the high PvO_2 , and the low $\%SaO_2$ and PVA in the dependent finger, we conclude that the PVA of the PEPG is determined mainly by venous pulse volume generated by shunting of arterial pulse via open arteriovenous (AV) anastomoses in the cutaneous circulation.

Key Words: MONITORING—plethysmograph, pulse oximeter. MEASUREMENT TECHNIQUES—pulse oximetry.

The plethysmograph is by definition a device for measuring and recording changes in volume of a part of the body, an organ, or the whole body. Since Hertzman and Speelman (1) described photoelectric plethysmography (PEPG) in 1937, the basic principles of its application have not changed, although various refinements have been added. Basically, the sensor in PEPG consists of a light source that emits a constant light level to the tissue, and a photoresistor that detects the degree of attenuation of light reflected from the tissue. Slight dilation and contraction of arterioles and capillaries during each blood pressure cycle are thought to attenuate the light reflection.

Therefore, PEPG requires the presence of a fairly high concentration of arterioles and capillaries near the surface of the skin, as found in the fingers and toes. Although PEPG has been used in numerous studies for 50 years, it is not clear what circulatory kinetics determine the pulse volume amplitude (PVA) of PEPG. In 1947, DeBaakey et al. (2) stated that PVA originates primarily within arteries and arterioles, but that over all volume changes within AV anastomoses, capillaries, veins, and venules are of greater importance than the pulse volumes in arteries and arterioles. In a review of PEPG, Challoner (3) concluded that the "tapping" mechanism involved in the derivation of the pulsatile component is complex and poorly understood, being influenced by both blood volume gradient during systole and diastole (pulse volume) and factors concerned with orientation of erythrocytes. He further concluded that the recorded pulse can be used as a reliable index of cutaneous flow. The present study sheds light upon the complex circulatory kinetics associated with PVA.

Presented in part at the annual meeting of the American Society of Anesthesiologists, San Francisco, California, October, 1985.

Received from the Department of Anesthesiology, University of Kansas, College of Health Sciences and Hospital. Accepted for publication June 30, 1986.

Address correspondence to Dr. Kim, Department of Anesthesiology, University of Kansas, College of Health Sciences and Hospital, 39th and Rainbow Boulevard, Kansas City, KS 66103.

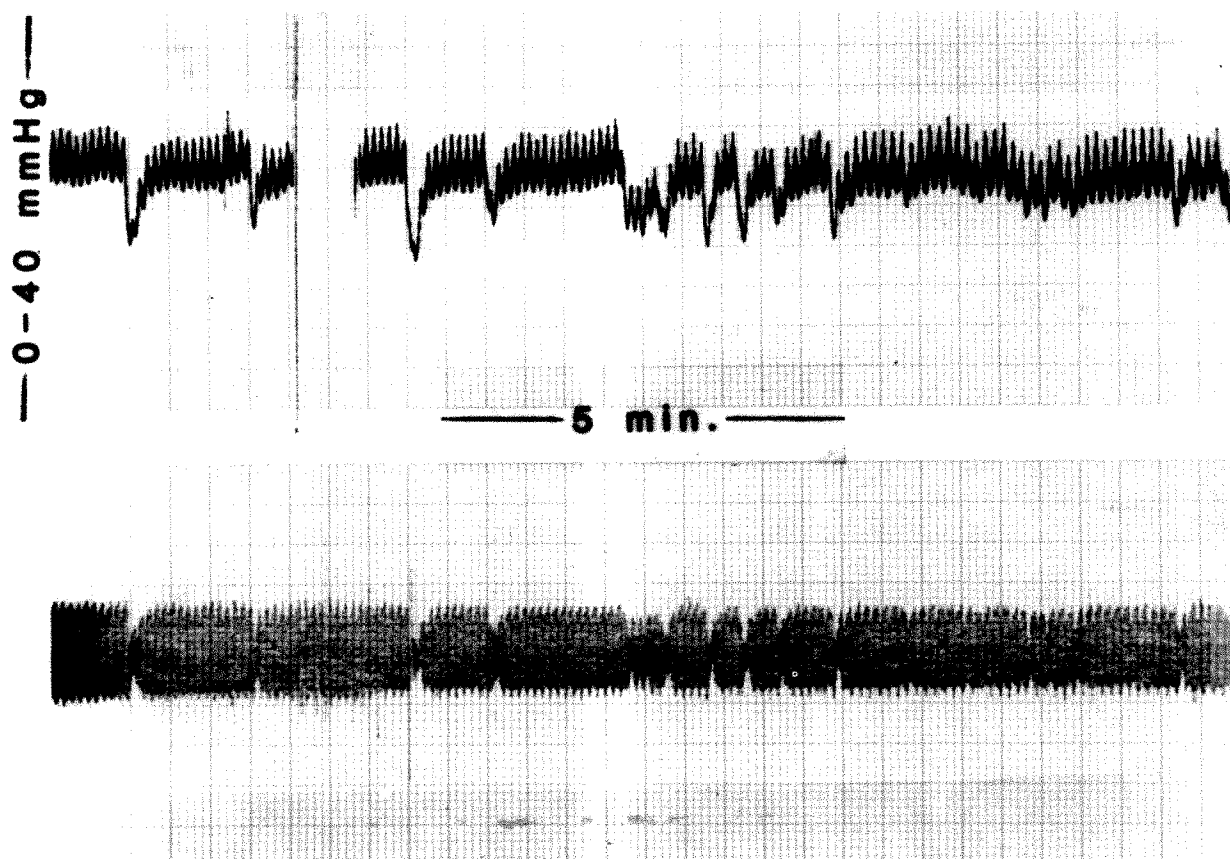


Figure 1. Simultaneous recordings of venous pressure (upper tracing) and pulse volume amplitude (lower tracing). Paper speed: 10 mm/min. On several occasions, as the pulse volume amplitudes acutely decreased, corresponding decreases occurred in venous pulse pressure and mean venous pressure.

Methods

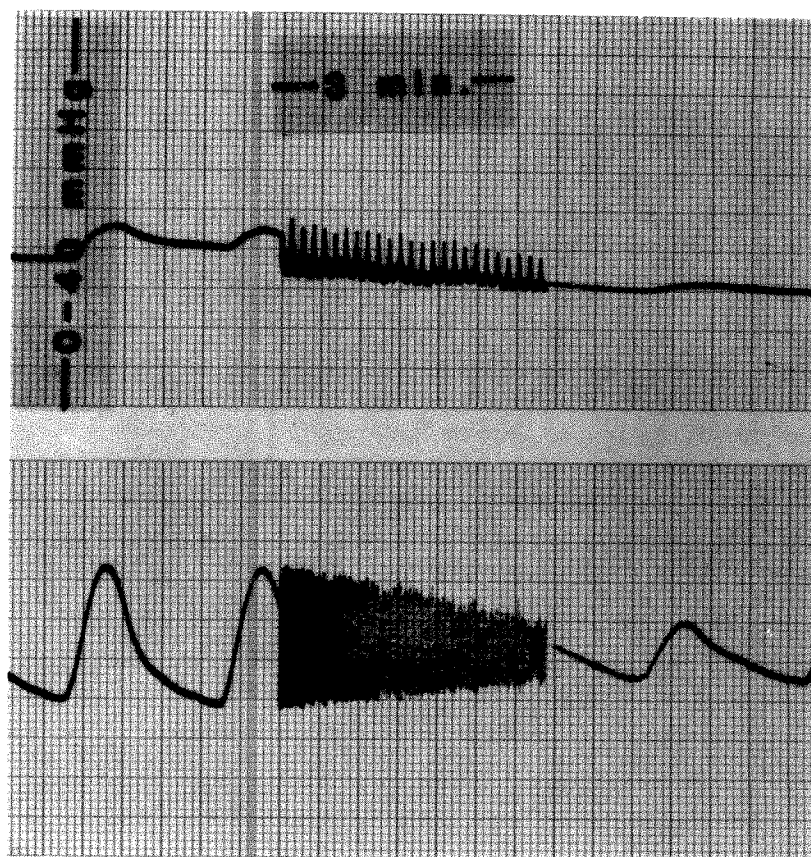
This study was approved by the institutional review board for human studies, and written consent was obtained from each patient. Twelve female and eight male patients participated in the study. Their mean age was 36 yr (range 21–67 yr) and their physical status was A.S.A. I or II. They underwent a variety of surgical procedures under general anesthesia. Anesthetic agents and techniques were not uniform, but all patients received one of the potent inhalation agents (isoflurane, enflurane, or halothane). As venodilation occurred after induction of anesthesia, a superficial vein on the dorsum of the proximal phalanx was cannulated with a 24-gauge, 1.6 cm catheter, the tip of which was directed distally. The venous pressure was measured with a pressure transducer (Gould P-50) positioned at the cannulated finger of the abducted arm on an arm board. A PEPG probe (Hewlett Packard, Model 14301A) was secured with a Velcro strip to the adjacent finger. Tracings of venous pressure

and PVA were displayed on the Hewlett Packard Monitor and were simultaneously recorded in slow speed, 10 mm/min, and intermittently at 25 mm/sec, using a two channel recorder (Hewlett Packard, Model 78172). Paired blood samples were drawn from the catheter to measure PvO_2 (Corning 175 Automatic pH/Blood Gas System). The first sample was obtained shortly after cannulation, when the PVA and venous pulse wave were significantly increased. The second sample was obtained when the PVA showed sustained narrowing and the venous pulse wave showed a flat line, usually as the patient was awakening from anesthesia. Fifteen paired PvO_2 values were included in the statistical analysis. Data from five patients were rejected either because patients were ventilated with FiO_2 levels outside the arbitrarily set range of 0.3–0.5, or because the paired samples were taken at different levels of FiO_2 .

For qualitative analysis, the acute or gradual changes in PVA caused by different surgical stimuli or levels of anesthesia were compared to the corresponding changes in venous pressures.

For quantitative analysis, we chose the section of recording that showed significant changes within a 15-min period. The highest PVA in this section was designated as high PVA, and $\frac{2}{3}$ and $\frac{1}{3}$ of the highest

Figure 2. Simultaneous recordings of venous pressure (upper tracing) and pulse volume amplitude (lower tracing). Paper speeds of middle and side sections are at 10 mm/min and at 25 mm/sec, respectively. As pulse volume amplitude decreases, venous pulse pressure and mean pressure also decrease. Respiratory deflections are shown as spikes in the venous pressure tracing.



PVA were designated middle PVA and low PVA, respectively. The venous pulse pressure and the mean pressure were measured at the corresponding high, middle, and low PVA levels. Pulse volume amplitude and venous pressure were expressed as mm and mm Hg respectively. Analysis of variance was utilized to compare the changes of pulse pressure and mean venous pressure as the high PVA changed to middle and low PVA. A $P < 0.05$ was considered to be statistically significant.

For the pulse oximeter study, %SaO₂ was measured with the pulse oximeter (Nellcor Pulse Oximeter, Model N-100, Nellcor Inc., Hayward, Ca) in 20 healthy human volunteers breathing room air. The skin temperature on the dorsum of the hand was measured and ensured to be more than 30°C. Using a disposable sensor, %SaO₂ was measured at the fingertip and at the finger base in both dependent and elevated positions. For the fingertip measurements, the sensor was placed as instructed in the manual. For the finger base measurements, the hypothenar skin just proximal to the fifth finger was sandwiched between the photodetector and light emitting diodes of the sensor. With the subject in a comfortable sitting position, the measuring hand was lowered below the heart level for a "dependent position" and was raised above the

head for an "elevated position." The values of %SaO₂ were recorded 30 sec after the pulse oximeter displayed a stable pulse volume signal and %SaO₂. The triplicated measurements were averaged at each site and position.

Results

Qualitative Analysis

As PVA acutely decreased in response to sudden changes in surgical stimuli, corresponding decrease in venous pulse pressure and mean pressure occurred simultaneously. This relationship between the PVA and venous pulse pressure was even more reliably predicted when the PVA showed a high amplitude (Fig. 1). The same trend of changes was observed as these two variables changed more gradually (Fig. 2)

Quantitative Analyses

The high PVA was averaged 17 ± 6 mm (mean \pm SD). As the high PVA regressed to the middle and low PVA levels, venous pulse pressure decreased from 4.3 ± 1.9 to 2.1 ± 1.3 and to 1.0 ± 0.6 mm Hg. These changes in mean venous pulse pressure were statis-

Table 1. Venous Pulse Pressure and Mean Pressure with High, Middle, and Low Pulse Volume Amplitudes

	High PVA ^a	Middle PVA	Low PVA	3.3 ± 1.5 mm
Pulse pressure (mm Hg) ^b	4.3 ± 1.9	2.1 ± 1.3	1.0 ± 0.6	flat line
Mean pressure (mm Hg)	26.4 ± 7.0	20.1 ± 6.3	20.0 ± 4.5	22.5 ± 6.9

Values are mean ± SD.

Abbreviation: PVA, pulse volume amplitude.

^aAmplitude of the high PVA; 17 ± 6 mm.^bPulse pressures in the three groups are statistically significantly different from each other ($P < 0.05$).

tically significant. However, the corresponding changes of mean venous pressure from 26.4 ± 7.0 to 20.1 ± 6.3 and 20.0 ± 4.5 mm Hg were not statistically significant. When the venous pulse wave became a flat line, even a slight increase in mean venous pressure was observed (Table 1). This may be attributed to obstruction of the constricted vein by the catheter. The PvO_2 values of the first and second samples were 132 ± 35 and 59 ± 12 mm Hg respectively.

Pulse Oximeter Study

The values of % SpO_2 in the dependent fingers were always equal to or less than % SpO_2 in the elevated fingers. Therefore, statistical significance was not sought. The average differences were 1.5% and 7.8% at the respective fingertip and finger base. The results are summarized in Table 2. The PVA during the measurement of % SpO_2 was lower in the dependent position than in the elevated position at both fingertip and finger base (Fig. 3).

Discussion

The superficial vein on the finger receives venous blood mainly from the skin. Circulation through the skin subserves tissue nutrition and thermoregulation. The blood flow for cutaneous nutrition is supplied by nutritive vascular channels, although this flow is so insignificant that nutritive blood flow plays almost no role in determining normal skin flow. In contrast, cutaneous flow can vary from 1 to as much as 150 ml/100 gm of skin per min in response to thermoregulatory stimuli. These variations are possible due to the special vascular structures for conduction of heat to cutaneous surface, including subdermal venous plexuses and AV anastomoses. The AV anastomoses, unique structures of the cutaneous circulation, are most abundant in the fingers and toes. The walls of these anastomoses have strong muscular coats that are innervated by sympathetic vasoconstrictor fibers. The simplest AV anastomoses are relatively straight channels connecting arterioles and venules with luminal diameters about 20–40 μ m. The more complex

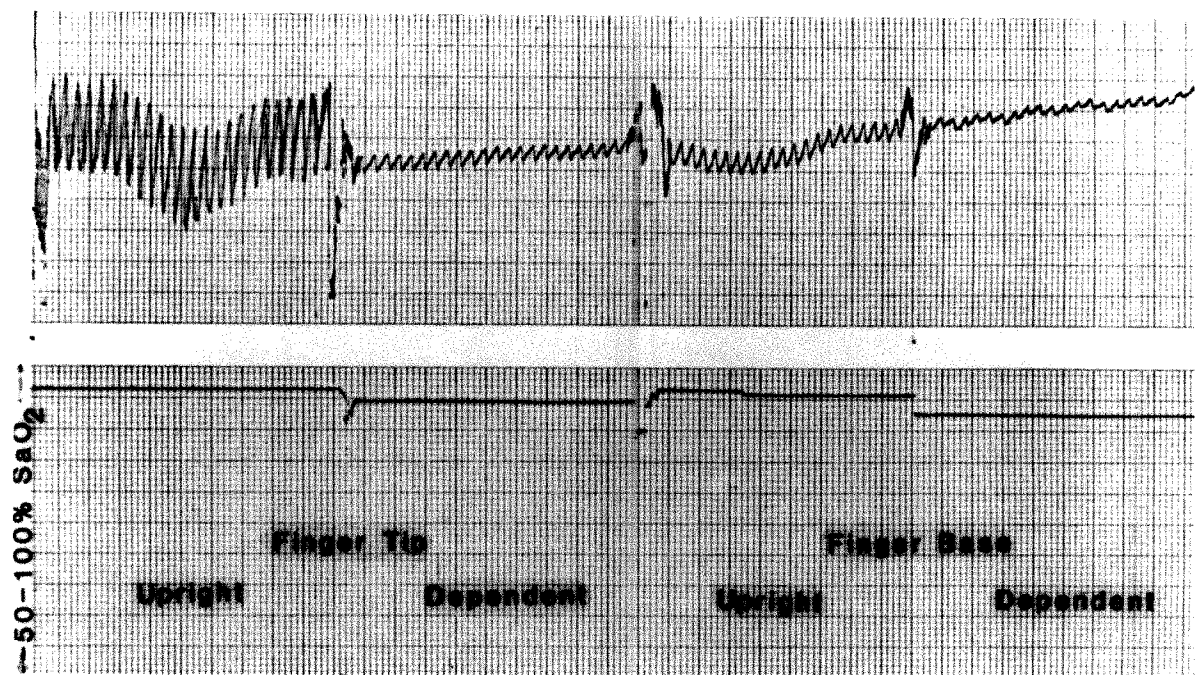
Table 2. Hemoglobin Saturations Measured by Pulse Oximetry in the Fingertip and Finger Base in Dependent and Elevated Positions

	Dependent position	Elevated position
Fingertip	96.1 ± 1.3%	97.6 ± 1.0%
Finger base	90.1 ± 3.9%	97.9 ± 1.4%

Values are mean ± SD.

AV anastomoses are tortuous and may have more than one vascular channel. The extreme form of this is an arteriovenous glomus (4–6).

The pulsatile venous pressure that we observed can be generated by direct transmission from a nearby artery, or by transmission of arterial pulse through open AV anastomoses. If the former mechanism is responsible for the pulsatile venous pressure, the artery should run in close proximity to the cannulated vein. Such intimate anatomic proximity between the artery and the vein is unlikely; the locations of most superficial small veins are extremely variable. Therefore, we postulated that the observed venous pulse was generated by transmission of arterial pulses via open AV anastomoses. If the AV shunting is responsible for the venous pulse, venous pulsations should depend upon the degree of shunting, arterial pulse pressure, compliance of the vein, central venous pressure, and the distance between the catheter tip and the sites of the major AV shunting. Because of these variables, venous pulse pressure cannot be used to quantitate the degree of AV shunting but could detect relative changes, especially when the degree of AV shunting is acutely altered. Similarly, the PVA of the PEPG can be used to detect relative change in cutaneous blood flow, but not in a quantitative manner. The purpose of the retrograde cannulation was to measure venous pressure close to where the AV anastomoses are most abundant. Cannulation of a more proximally located larger vein did not show a venous pulse, probably because shunted arterial pulse becomes damped by distance. Retrograde cannulation of a small vein could obstruct flow; therefore, one might conclude that in our studies venous pulse pressure was created by obstruction as with venous oc-



clusion plethysmography. Unlike the venous occlusion plethysmograph, venous obstruction in our studies was limited to a single vein, which should have many collateral channels that prevent back pressure. Our findings of increased venous pulse pressure and increased mean pressure in dilated veins do not correlate with obstruction, because obstruction should more likely occur in constricted veins. However, as the venous pulse wave became a flat line during recovery from anesthesia, we noted that the mean venous pressure tended to increase, which could be caused by venous obstruction by the catheter.

Venous pressure should be measured at the reference point of pressure measurement, clinically at the midaxillary line in the supine position. To avoid the additional extension tubing, the reference point was chosen at the finger of the abducted arm. This position of the transducer should be close to the clinical reference point. The normal pressure in the peripheral veins is usually 4–9 mm Hg greater than right atrial pressure. Even though slight elevation of the right atrial pressure may have occurred in our anesthetized and artificially ventilated patients, our values of venous pressures, over 20 mm Hg, are unexpectedly high. However, these levels of venous pressure become understandable, if a significant AV shunting is assumed.

One of us (J-MK) (7,8) reported that sympathetic denervation associated with spinal or epidural anesthesia increased PVA in the toe, and subsequent recovery decreased PVA. Changes in finger PVA during the perioperative period were also measured by John-

Figure 3. Recordings of pulse volume amplitude (upper tracing) and hemoglobin saturation (lower tracing). Pulse volume amplitude and hemoglobin saturation values are always greater in the elevated position than in the dependent position both at the fingertip and at the finger base.

stone (9). He observed that PVA increased in most undisturbed unconscious patients after induction of anesthesia, and the increased PVA showed either transient or persistent decreases in response to different surgical stimuli or levels of anesthesia. He postulated that the decrease in PVA resulted from reflex vasoconstriction caused by α -adrenergic stimulation. Johnstone's findings were confirmed in our anesthetized patients. The increased PVA indicates that the difference in blood volume during systole and diastole (pulse volume) is exaggerated. Increased cutaneous blood flow by arterial or arteriolar dilatation is in itself an insufficient explanation for the increase in PVA, because both systolic and diastolic volume should be affected by the vasodilation. However, it is well known that sympathetic denervation opens AV anastomoses. Cronenwett et al. (10) found that sympathectomy increased flow through AV anastomoses more than four times above baseline levels in the dog. Electrical stimulation of the distal end of the transected sympathetic chain immediately and reversibly decreased flow through AV anastomoses. Because high pressure arterial flow is shunted through open AV anastomoses into more compliant low pressure veins, the pulse volume created in the veins should be greatly amplified. Sluiter et al. (11) stated that for

the same variations in pressure, the changes in the venous vascular volume are much greater than those in the arterial bed, because venous compliance is greater than arterial compliance by a factor of ten or more.

Because values of PvO_2 depend upon the degree of AV shunting, PvO_2 , venous pressure and PVA should follow a similar trend as the degree of shunting changes. This was demonstrated in our study. High PvO_2 values during similar conditions of general anesthesia and FtO_2 were reported by Williamson and Munson (12). Their mean PaO_2 value was 147 mm Hg and the mean arteriovenous oxygen tension difference was 48.8 mm Hg. The venous sample was obtained from the dorsum of the hand in their study.

Using the principles of spectrophotometric oximetry and PEPG, the pulse oximeter continuously monitors arterial $\%SaO_2$ and pulse. Because the $\%SaO_2$ is derived only from a pulsating fraction of the blood, the measured value is assumed to be that of the arterial inflow. To exclude interference from surrounding venous blood, venous blood should not pulsate. Even though our observed pulsatile venous pressure is assumed to be generated by direct or indirect transmission from nearby arteries, its intervention as a pulsatile component of the finger pulse should add a significant error in the measurement, because the volume of unsaturated venous blood is much greater than the volume of arterial blood. However, the pulse oximeter yields an appropriate value in most clinical situations, except when vascular pulsations are significantly reduced by hypothermia, hypotension, or infusion of vasoconstrictor drugs. This limitation claimed to reduce the ability of pulse oximetry to measure saturation (13). The capability and limitation of the pulse oximeter can be easily explained by our present findings. The venous blood in the skin is composed of two fractions: the shunted arterial blood, which is highly saturated and pulsatile, and the true venous blood, which is drained from the capillaries after tissue perfusion (nutritive vascular channels) and is therefore desaturated and nonpulsatile. If the proportion of shunted arterial blood greatly exceeds the true venous blood, the pulse oximeter should yield a value close to a true arterial $\%SaO_2$. If the AV shunting is severely restricted by increased sympathetic tone, the increased proportion of the true venous blood should result in a falsely low value of $\%SaO_2$. The resulting factitiously low value created by reduced vascular pulsation is comparable to the decrease in PvO_2 seen in our patients during emergence from anesthesia. The values of $\%SaO_2$ measured by a pulse oximeter and measured directly from arterial blood were compared in previous studies. The correlation coefficient was 0.98 in the study on healthy human

volunteers by Yelderman and New (13), but it was 0.72 when data were collected from critically ill patients in the intensive care unit by Kim et al. (14). We postulated that this discrepancy was created by a difference in sympathetic tone between the healthy volunteers and the critically ill patients.

The decreased $\%SaO_2$ and PVA in the dependent finger could be explained by venous congestion. Decreased compliance of the congested vein should limit the pulsation of the finger. Because the pressure gradient favors forward movement, the shunted fraction of arterial blood should drain out from the congested vein faster than the true venous blood, which should decrease the $\%SaO_2$ in the dependent finger by increasing the fraction of the true venous blood.

Venous blood at the fingertip comes mainly from cutaneous tissue, which is known to have abundant AV anastomoses, and so the $\%SaO_2$ should not be greatly affected by the position. On the other hand, blood coming from extracutaneous tissues, such as the muscle, should join the venous blood at the finger base. Because AV anastomoses are not known to be present in the skeletal muscles, the fraction of true venous blood at the finger base should be especially increased by venous congestion. Therefore, the $\%SaO_2$ should be significantly affected by the position. Slight cyanosis observed on the dependent palm may be comparable to the low value of $\%SaO_2$ observed in the dependent finger base. The cyanotic appearance is usually exaggerated in a cold hand; therefore, we ensured that the skin temperature of our volunteers exceeded 30°C to preserve AV shunting.

In conclusion, the PVA of the PEPG appears to be influenced by pulse volume in the capacitance vessels generated by AV shunting. This new concept will help in understanding $\%SaO_2$ measured by pulse oximetry.

We wish to express our gratitude to Mr. David E. Cobb, Department of Physiological Monitoring and Instrumentation, for his technical assistance throughout the study and Mrs. Didi Cato for preparation of the manuscript.

References

1. Hertzman AB, Speelman CR. Observation on the finger volume pulse recorded photo-electrically. *Am J Physiol* 1937;119:334-5.
2. DeBakey ME, Burch G, Ray T, Ochsner A. The "borrowing-lending" hemodynamic phenomenon (hemometakinesia) and its therapeutic application in peripheral vascular disturbances. *Ann Surg* 1947;126:850-65.
3. Challoner AVJ. Photoelectric plethysmography for estimating cutaneous blood flow. In: Rolfe P, ed. *Noninvasive physiological measurements*. Vol. 1. London: Academic Press, 1979:125-51.

4. Ganong WF. Review of medical physiology. 12th ed. Los Altos: Lange Medical Publications, 1985:509-10.
5. Guyton AC. Textbook of medical physiology. 5th ed. Philadelphia: W.B. Saunders, 1976:379.
6. Spark HV. Skin and muscle. In: Johnson PC, ed. Peripheral circulation. New York: Wiley Medical Publications, 1978: 193-209.
7. Kim J-M, Arakawa K, VonLintel T. Use of the pulse-wave monitor as a measurement of diagnostic sympathetic block and of surgical sympathectomy. *Anesth Analg* 1975;54:289-96.
8. Kim J-M, LaSalle AD, Parmley RT. Sympathetic recovery following lumbar epidural and spinal analgesia. *Anesth Analg* 1977;56:352-5.
9. Johnstone M. Digital vasodilation: a sign of anaesthesia. *Br J Anaesth* 1974;46:414-9.
10. Cromewett JL, Zelenock GB, Whitehouse WM, Stanley JC, Lindenauer SM. The effect of sympathetic innervation on canine muscle and skin blood flow. *Arch Surg* 1983;118:420-4.
11. Sluiter ER, Rowaan CJ, Doxlas JC, Nijboer JA, Horritsma F, Blom JA, Beneken JEW. Peak-to-peak detector for the arterial pulsations in the plethysmogram II: results of its use during anaesthesia. *Med Biol Eng Comput* 1981;19:267-70.
12. Williamson D, Munson E. Correlation of peripheral venous arterial blood gas values during general anesthesia. *Anesth Analg* 1982;61:950-2.
13. Yelderian M, New W Jr. Evaluation of pulse oximetry. *Anesthesiology* 1983;59:349-52.
14. Kim SK, Baidwan BS, Petty TL. Clinical evaluation of a new finger oximeter. *Crit Care Med* 1984;12:910-12.

Cardiovascular and Neuromuscular Responses to High-dose Pancuronium–Metocurine in Pediatric Burned and Reconstructive Patients

Judy Hagen, MD, Jeevendra Martyn, MD, S. K. Szyfelbein, MD, and
Nishan G. Goudsouzian, MD

HAGEN J, MARTYN J, SZYFELBEIN SK, GOUDSOUZIAN NG. Cardiovascular and neuromuscular responses to high-dose pancuronium–metocurine in pediatric burned and reconstructive patients. *Anesth Analg* 1986;65:1340-4.

The efficacy of the combined use of pancuronium and metocurine (Pm–MTC) in high doses to produce rapid-onset muscle paralysis was evaluated in 15 patients with acute burns and 18 recovered burned patients scheduled for reconstructive surgery. Two and three times the previously determined ED₉₅ of the combination for each group was used. (ED₉₅ for Pm–MTC combination is 0.032/0.129 mg/kg for acute burns and 0.013/0.051 mg/kg for reconstructive patients.) Doubling ED₉₅ produced 95% paralysis in 3.1 ± 0.9 min in acutely burned children and in 4.3 ± 0.7 min in reconstructive children (mean ± SEM). These onset times were not significantly different from each other. Tripling the ED₉₅ of the combination in burned children reduced the onset time to 1.3 ± 0.14 min, but this was not significantly different from 2 × ED₉₅ onset time in burned patients. The administration of 3 × ED₉₅ to the reconstructive group, however, resulted in a significantly more rapid onset time of 1.8 ± 0.4 min compared with 2 × ED₉₅ in the same population. With 3 × ED₉₅ the onset times between burn and reconstructive patients were not significantly different. Time for recovery of twitch to 25% of control twitch height (75% twitch depression) was significantly prolonged in burned patients compared with reconstructive patients for equipotent doses administered. Although the occasional patient showed prominent changes in heart rate and blood pressure, overall cardiovascular stability was impressive. Therefore, high doses of Pm–MTC combination can be used in combination to produce more rapid onset of paralysis in burned patients and may also represent an alternative to succinylcholine in other situations wherein there is risk of succinylcholine-induced hyperkalemia. This technique does not provide as rapid onset of paralysis as succinylcholine.

Key Words: ANESTHESIA—pediatric. COMPLICATIONS—burns. NEUROMUSCULAR RELAXANTS—pancuronium, metocurine.

Succinylcholine continues to be the drug of choice for rapid-onset neuromuscular (NM) paralysis in clinical emergencies, such as laryngospasm and the full stomach. In certain pathologic states, such as burns and denervation syndromes, however, the depolarizing NM relaxant succinylcholine is contraindicated because of the potential for lethal hyperkalemia (1).

Increasing the dose of nondepolarizing NM relax-

ants can be used to produce rapid-onset paralysis in normal patients (2). Even in normal patients, however, these high doses may produce unacceptable cardiovascular effects. In pathologic states such as burns, immobilization, and denervation, the dose and serum concentration requirements for effective paralysis are several-fold higher than normal (3,4). Consequently, to achieve rapid-onset of NM paralysis in patients with such pathologic states, even larger doses of nondepolarizing muscle relaxants may be required. If these doses are administered as a bolus, as often necessary in emergency situations, undue cardiovascular effects are likely to occur, as has been shown with high-dose pancuronium (Pm) (5). The combination of high-dose pancuronium and metocurine (Pm–MTC), on the other hand, has been shown in adults to produce rapid onset of paralysis with minimal changes in heart rate and blood pressure (5). These desirable features can

Supported by grants from the Shriners Burns Institute and from NIH GM 31569 and GM 21700.

Received from the Department of Anesthesiology, Harvard Medical School and the Anesthesia Services of Massachusetts General Hospital and Shriners Burns Institute, Boston, Massachusetts. Accepted for publication June 24, 1986.

Address correspondence to Dr. Martyn, Department of Anesthesiology, Massachusetts General Hospital, Boston, MA 02114.

be used to advantage in patients in whom succinylcholine is contraindicated. The present study evaluates the efficacy and safety of high-dose Pm-MTC in children with acute burns and in children presenting for reconstructive surgery.

Methods

The study was approved by the Human Studies Committee of our institution, and informed consent was obtained. We studied 15 patients with acute burns and 18 recovered burned patients who were scheduled for reconstructive surgery. In the latter group, more than 2 years had elapsed since recovery from burn. The clinical variables are summarized in Table 1.

In all patients anesthesia was induced by intravenous thiopental (4–7 mg/kg), or rectal methohexital (25–30 mg/kg), and maintained on nitrous oxide plus oxygen and narcotic. Morphine or fentanyl was administered as clinically indicated. Neuromuscular transmission was studied by stimulation of the ulnar nerve using 22-gauge needles inserted under the skin. Supramaximal pulses lasting 0.2 msec were delivered at a frequency of 0.15 Hz. Thumb adduction was recorded through a force-displacement transducer (FT03 and FT10).

After induction of anesthesia after heart rate, blood pressure, and twitch tension had stabilized, two or three times the ED₉₅ of the Pm-MTC combination was administered. Doses of Pm and MTC for combined administration were calculated on the basis of a previous study in this population. In children undergoing reconstructive surgery the ED₉₅ was 0.013 mg/kg for Pm and 0.051 mg/kg for MTC (6). In burned children the ED₉₅ for combined administration was 0.032 mg/kg for Pm and 0.129 mg/kg for MTC (6). The doses are indicated in Table 2. The 2 × ED₉₅ studies were completed in each group prior to initiation of the 3 × ED₉₅ studies. Heart rate and systolic blood pressures were measured at baseline and at 0.5, 1, 3, and 5 min after the bolus. Endotracheal intubation was performed after this period. Heart rate was monitored via the ECG tracing. In burned children the blood pressure was measured via an indwelling intraarterial catheter, whereas, in reconstructive children a blood pressure cuff was used. After the administration of relaxant the onset time to 95% twitch depression (5% of control twitch height) and the time for spontaneous recovery from maximal depression to 25% of the control twitch height (75% depression) were also recorded.

The data on blood pressure and heart rate were analyzed according to techniques of analysis of var-

Table 1. Clinical Variables

	Reconstructive (n = 18)	Burns (n = 15)
Age (yr)	9.3 ± 1.3	10.0 ± 1.1
Weight (kg)	40.2 ± 4.5	43.5 ± 6.1
Time after burn (weeks)	270.0 ± 52	3.6 ± 1.4
Body surface area burn (%)	—	65.3 ± 6.2

Mean ± SEM.

iance appropriate to the repeated-measures design (7,8). Intragroup comparisons between mean baseline values and subsequent values were made using Dunnett's test, where appropriate, and Bonferroni *t*-statistics otherwise. All calculations were subject to a experimental error rate that remained constant at 0.1 for the combined set of 16 comparisons. The data on peak effect and recovery times were analyzed by one-way analysis of variance, followed by Hochberg's GT studentized maximum modulus procedure (7,8).

Results

The NM responses to high-dose Pm-MTC in burned and reconstructive patients are tabulated in Table 3. In both groups, despite doubling the ED₉₅, the effect on time of onset (to 95% twitch depression) remained >3 min. Tripling the ED₉₅ dose resulted in statistically more rapid onset of twitch depression in reconstructive surgery patients compared with 2 × ED₉₅ in the same group. In the burned patients with 3 × ED₉₅ the mean onset time was reduced but not statistically significantly so, compared with 2 × ED₉₅. When burned children were compared with reconstructive children when equipotent doses were administered (e.g., 3 × ED₉₅ vs 3 × ED₉₅), the times of onset also were not significantly different between groups with both doses. In the reconstructive group the administration of high doses resulted in a significantly longer recovery time. Within the burn group the higher dose did not result in significantly longer recovery time. When the recovery time in the burn group is compared with the reconstructive group for equipotent dose (e.g., 2 × ED₉₅ vs 2 × ED₉₅) the burned patients had a significant more prolonged recovery time.

The mean cardiovascular responses during the observation period following high-dose Pm-MTC are shown in Tables 3 and 4. There were no significant changes in mean blood pressure. In contrast to blood pressure, significant increases in heart rate were recorded in all groups at some time during the observation period (Table 4, Fig. 1). Figure 1 shows the maximum increase in heart rate and decrease in blood

Table 2. Neuromuscular Pharmacodynamics

	Reconstructive		Burns	
	2 × ED ₉₅ (n = 13)	3 × ED ₉₅ (n = 5)	2 × ED ₉₅ (n = 9)	3 × ED ₉₅ (n = 6)
Dose Pm/MTC (mg/kg)	0.026/0.102	0.039/0.153	0.064/0.258	0.96/0.387
Time to 95% depression (min)	4.3 ± 0.7	1.8 ± 0.4 ^a	3.1 ± 0.9	1.3 ± 0.14
Time to 25% recovery (min)	46.4 ± 4.2	85.5 ± 17.6 ^a	112.9 ± 18.1 ^b	152 ± 32.4 ^c

Mean ± SEM.

^aP < 0.05 2 × ED₉₅ reconstructive vs 3 × ED₉₅ reconstructive.^bP < 0.05 2 × ED₉₅ burn vs 2 × ED₉₅ reconstructive.^cP < 0.05 3 × ED₉₅ burn vs 3 × ED₉₅ reconstructive.

Table 3. Changes in Systolic Blood Pressure

	Blood pressure				
	Control (mm Hg)	0.5 min (mm Hg)	1 min (mm Hg)	3 min (mm Hg)	5 min (mm Hg)
Reconstructive					
2 × ED ₉₅	98.0 ± 4.8	95.2 ± 5.3	98.8 ± 4.0	98.2 ± 4.1	102.6 ± 3.6
3 × ED ₉₅	93.4 ± 5.8	92.4 ± 4.9	95.0 ± 4.1	94.0 ± 4.1	96.6 ± 3.2
Burns					
2 × ED ₉₅	112.9 ± 4.9	111.9 ± 5.4	107.4 ± 5.0	105.8 ± 6.7	103.9 ± 6.0
3 × ED ₉₅	114.0 ± 9.9	110.2 ± 5.8	105.2 ± 5.8	110.7 ± 7.4	115.7 ± 8.1

Mean ± SEM.

Table 4. Changes in Heart Rate

	Heart Rates				
	Control	0.5 min	1 min	3 min	5 min
Reconstructive					
2 × ED ₉₅	91.2 ± 4.9	97.8 ± 5.4 ^a	101.2 ± 4.5 ^a	102.5 ± 4.4 ^a	105.3 ± 4.3 ^a
3 × ED ₉₅	99.4 ± 14.4	107.2 ± 14.5 ^a	106.8 ± 13.7	105.8 ± 14.0	105.4 ± 13.3
Burns					
2 × ED ₉₅	126.7 ± 8.2	131.0 ± 8.4	131.7 ± 6.4	134.8 ± 6.7	139.3 ± 5.4 ^a
3 × ED ₉₅	132.2 ± 5.8	137.8 ± 6.0	138.8 ± 6.5	141.0 ± 6.4 ^a	142.7 ± 6.2 ^a

Mean ± SEM (% change).

^aP < 0.05 compared to control (baseline).

pressure for each patient at *any time* during the observation period. Despite the lack of change in mean blood pressure, in the occasional patient there was a marked drop in systolic blood pressure, but at no time was therapy required.

Discussion

Contraindications to the depolarizing NM relaxant succinylcholine in conditions such as burns, denervation, multiple trauma, and neurological disease are well documented (1). At the same time, the ED₉₅ for alternative nondepolarizing NM relaxants is markedly

increased. As much as three to ten times the normal doses or serum concentrations may be required (3,4,6). Moreover, these patients may often present with emergent problems, such as laryngospasm or a full stomach, which require immediate, rapid induction of paralysis. This study documents that NM paralysis can be more rapidly produced with high-dose than with low-dose Pm-MTC. As a whole, the patients demonstrated good stability with respect to blood pressure. The moderate increase in heart rate in all patients at some time during the observation period may be desirable in burned children. The increased heart rate may have increased cardiac output and thus

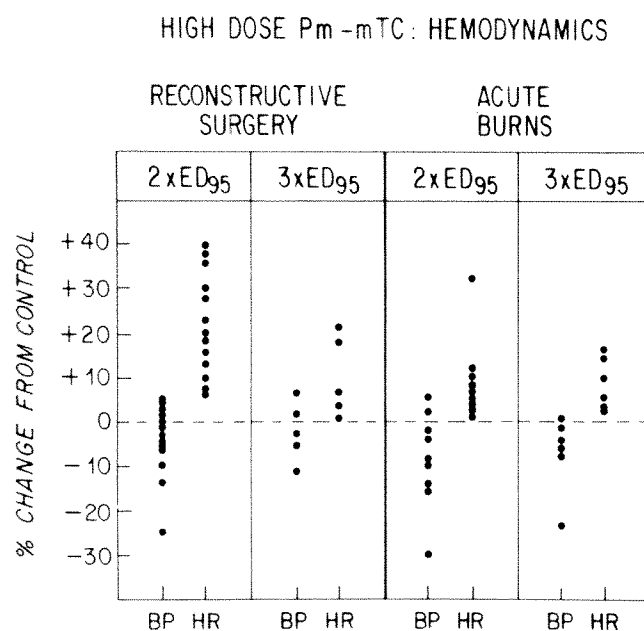


Figure 1. Shown in this diagram are the maximal increase in heart rate and the lowest drop in blood pressure occurring at any time throughout the observation period. Individual patients may show prominent changes in these parameters.

prevented changes in blood pressure, a useful and necessary feature in the hypermetabolic burned patient.

The relative absence of cardiovascular effects despite the high doses used is noteworthy. The absence of significant changes in blood pressure is particularly important in the burned children because of the critical nature of their illness (9). The present results are particularly impressive, bearing in mind that $3 \times \text{ED}_{95}$ dose for burned patients is approximately seven times the ED_{95} dose for normal patients. The dose of 0.096 mg/kg Pm administered to burned children is approximately twice the ED_{95} for a normal child (10), and 0.387 mg/kg MTC is approximately twice the ED_{95} (0.2 mg/kg) for normal children when the drugs are administered alone (11). That is, twice the ED_{95} of each drug was administered in combination in the present study, and no significant change in blood pressure or clinically significant change in heart rate was noted. Whether or not such stability in the cardiovascular system will be seen in young adults and older patients with burns, however, cannot be assumed on the basis of the present data.

Lebowitz et al. have documented the hemodynamic and pharmacodynamic effects of Pm alone and the Pm-MTC combination at twice the ED_{95} doses in normal adult patients. The ED_{95} for combined Pm-MTC administration in adult patients with 0.018 mg/kg for Pm plus 0.072 mg/kg for MTC (5). In that study, when

0.15 mg/kg Pm was administered alone, mean systemic blood pressure increased slightly but was not significantly different from controls, whereas, the heart rate increased significantly. With $2 \times \text{ED}_{95}$ combination, both mean systemic blood pressure and heart rate remained essentially unchanged. In our study in children, Pm and MTC were used in the same 1:4 ratio (12). When $2 \times \text{ED}_{95}$ doses were administered, time to 95% twitch depression was 4.3 ± 0.7 min in the reconstructive group and at 3.1 ± 0.9 min in the burned group. This result contrasts with $2 \times \text{ED}_{95}$ doses of Pm-MTC administered to normal adults, which resulted in 99% twitch suppression in 2.6 ± 0.6 min (5). When the dose was increased to $3 \times \text{ED}_{95}$ the onset of twitch suppression was markedly enhanced, resulting in adequate relaxation by 1.8 min in the reconstructive group. In the burned group the onset time compared with $2 \times \text{ED}_{95}$ did not reach statistical significance. For obvious reasons the onset time for intravenous succinylcholine has not been documented in burned children, but in healthy patients it occurs in less than 1 min (50 sec). In this respect, therefore, onset times with 2 and $3 \times \text{ED}_{95}$ Pm-MTC is not comparable with the onset time of succinylcholine.

It has been documented previously that with the ED_{95} dose of Pm-MTC, the 5-25% recovery time (95% depression to 75% depression) is approximately 15 min in reconstructive patients and 20 min in burned pediatric patients (6). In this study, when $2 \times \text{ED}_{95}$ doses were administered to these children, recovery time to 25% of control twitch height was more than tripled in both groups compared with ED_{95} recovery time reported previously (6). When $3 \times \text{ED}_{95}$ doses were administered the time for recovery to 25% of control twitch height was markedly prolonged to 85.5 ± 17 min in the reconstructive group, and to 152 ± 32 min in the burned group. For both doses the recovery time in burned children was significantly prolonged compared with reconstructive children when equipotent doses were compared. That 5-25% recovery was prolonged in burned patients after such a large dose can be ascribed to any of the following causes: a) Increased binding of muscle relaxants occurs after burn injury (13). Because only the free fraction of drug is filtered across the glomerulus of the kidney, the increased binding (decreased free fraction) of muscle relaxants results in decreased renal elimination of drug, which, in turn, can result in a prolonged twitch recovery time; b) the higher dose itself may contribute to the prolonged recovery time; and c) depressed liver function and drug metabolism seen after burn injury (14) may also play a role in prolonging recovery of normal twitch response.

This study documents a technique for the administration of nondepolarizing relaxants that can effectively increase the time of onset of paralysis with virtually no cardiovascular changes. Although the technique requires a series of calculations to arrive at the appropriate dose and although the Pm-MTC combination is associated with a prolonged duration of action. The technique has great value and application in certain clinical emergencies, as described above. An easy way to remember these doses for acute burned patients is to use standard single adult doses for intubation (Pm 0.1 mg/kg, MTC 0.4 mg/kg), but use them in combination. In the reconstructive patients, about half the above dosage could be satisfactory. Although this study was performed on burned patients, this same dosage regimen is possibly applicable to other conditions in which succinylcholine is contraindicated but in which there is resistance to the effects of nondepolarizing NM blockers.

David Hoaglin provided the statistical expertise in the analysis of data.

References

1. Gronert GA, Theye RA. Pathophysiology of hyperkalemia induced by succinylcholine. *Anesthesiology* 1975;43:89-99.
2. Brown E, Krishnaprasad D, Smiler BG. Pancuronium for rapid induction technique for tracheal intubation. *Can Anaesth Soc J* 1979;26:489-91.
3. Martyn JAJ, Szyfelbein SK, Ali HH, Matteo RS, Savarese JJ. Increased d-tubocurarine requirement following burn injury. *Anesthesiology* 1980;52:352-5.
4. Gronert GA, Matteo RS, Perkins S. Canine gastrocnemius disuse atrophy: resistance to paralysis by dimethyltubocurarine. *J Appl Physiol* 1984;57:1502-6.
5. Lebowitz PW, Ramsey FM, Savarese JJ, Ali HH, deBros FM. Combination of pancuronium and metocurine: neuromuscular and hemodynamic advantages over pancuronium. *Anesth Analg* 1981;60:12-5.
6. Satwicz PR, Martyn JAJ, Szyfelbein SK, Firestone S. Potentiation of neuromuscular blockade using a combination of pancuronium and dimethyltubocurarine. *Br J Anaesth* 1984;56:479-84.
7. Miller RG. Simultaneous statistical inference. New York: McGraw-Hill Co., 1966;67-70, 76-81.
8. Milliken GA, Johnson DE. Analysis of messy data. Belmont, CA: Life Time Learning Publications, 1984:384-407.
9. Martyn JAJ, Snider MT, Szyfelbein SK, Burke JF, Laver MB. Right ventricular dysfunction in acute thermal injury. *Ann Surg* 1980;191:330-5.
10. Goudsouzian NG, Ryan JF, Savarese JJ. The neuromuscular effects of pancuronium in infants and children. *Anesthesiology* 1974;42:95-8.
11. Goudsouzian NG, Liu LMP, Savarese JJ. Metocurine requirements in infants and children: Neuromuscular and clinical effects. *Anesthesiology* 1978;49:266-9.
12. Martyn JAJ, Liu LMP, Szyfelbein SK, Ambalavanar E, Goudsouzian NG. The neuromuscular effects of pancuronium in burned children. *Anesthesiology* 1983;59:561-4.
13. Leibel WS, Martyn JAJ, Szyfelbein SK, Miller KW. Elevated plasma binding cannot account for the burn related d-tubocurarine hyposensitivity. *Anesthesiology* 1981;54:378-82.
14. Martyn JAJ, Greenblatt KD, Quinby WC. Diazepam kinetics in patients with severe burns. *Anesth Analg* 1983;62:293-7.

Review Article

Electroconvulsive Therapy and Anesthetic Considerations

George Y. Gaines III, MD, and D. Ian Rees, MB, BCH

Electroconvulsive therapy (ECT) has developed into a widely recognized but frequently controversial treatment modality in psychiatric practice (1,2). In the United Kingdom, 200,000 treatments are administered per year (3). American studies show that about 4% of psychiatric admissions are for the purpose of ECT (4), the number of ECT treatments now numbering approximately 100,000 per year (5).

To provide effective anesthesia to patients who may benefit from ECT, the anesthesiologist must be equipped with an in-depth knowledge and technical skill in this segment of anesthetic practice. The purpose of this report is to acquaint the anesthesiologist with relevant aspects of ECT and to review current knowledge on the effects of anesthetic agents on the effectiveness of ECT, together with considerations for the administration of anesthesia for ECT therapy.

Historical Perspective

Beginning in 1934, large numbers of schizophrenic patients were treated with chemically induced seizures based on the erroneous belief that schizophrenia and epilepsy were antagonistic, and on the valid finding that patients with both disorders experience an improvement in schizophrenia after spontaneous generalized epileptic seizures. Sakee used insulin overdose (6), and Meduna pentylenetetrazol (Metrazol) (7) to produce the seizures. Although more successful than alternative treatments, the technique of inducing seizures was less than satisfactory, with seizures frequently delayed or even absent. In addition, a prolonged state of cerebral hyperexcitability occasionally led to spontaneous postictal seizures.

In 1938, Cereletti and Bini used a simple technique to induce seizures in animals by the application of an electrical stimulus during the study of the mechanism of generalized epilepsy. After their successful use of the method clinically (8), the use of ECT spread quickly and soon became established in the United States as the dominant somatic therapy for schizophrenia (9).

In 1940, Bennett described the use of curare for modifying drug-induced convulsions, not electroconvulsions as stated in many textbooks. Curare was subsequently used in ECT, but its use did not become commonplace for several years (10). During this period, Bellett in 1941 (11), Kolb in 1946 (12), and Altschule in 1947 (13), with their associates, reported on the cardiovascular complications after convulsions.

Further advances in convulsion modification came with the introduction of gallamine by Hughenard and Bone in 1949 (14) and the introduction of succinylcholine by Holmberg and Thesleff in 1951 (15). It is of note that reports on the use of these drugs in ECT preceded papers on their use in general anesthesia. Finally, in 1959, Friedman reported the use of intravenous methohexital for modification of seizure activity (16). By the 1960s the technique of using short-acting intravenous barbiturates and depolarizing muscle relaxants became accepted as a simple, safe regime in order to produce modified ECT (17).

Clinical Indications for ECT

Depressive States

The main role of ECT in contemporary practice is the treatment of depressed patients who have failed to respond to an adequate course of antidepressant drugs. Several qualifications, however, must be mentioned. Many studies have indicated that patients with classical symptoms of "endogenous" depression (severe, acute onset of depression, diurnal mood variation, sleep disturbance, and loss of weight, appetite, and

Received from the Department of Anesthesiology, University of Texas Health Science Center, Parkland Memorial Hospital, Dallas, Texas. Accepted for publication June 27, 1986.

Address correspondence to Dr. Gaines, Department of Anesthesiology, University of Texas Health Science Center, Parkland Memorial Hospital, 5323 Harry Hines Blvd., Dallas, TX 75235.

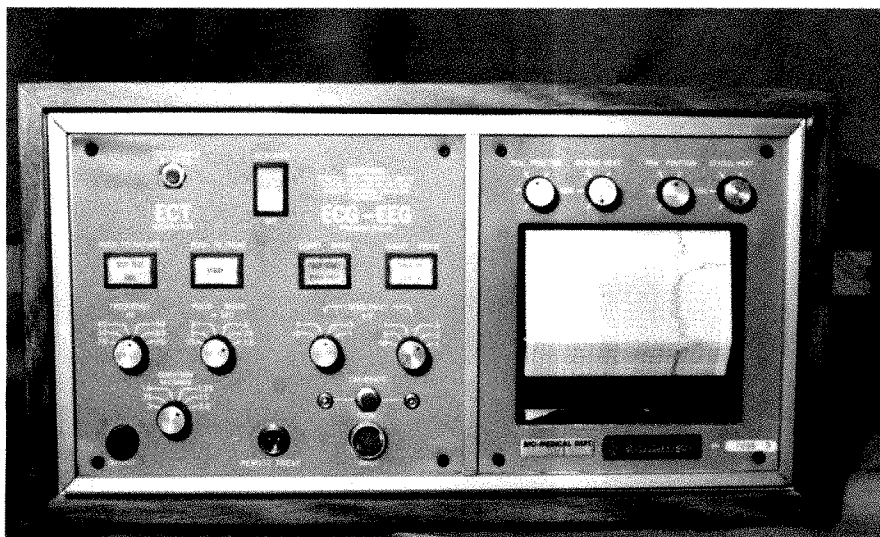


Figure 1. Multiple-monitored electroconvulsive therapy machine.

libido) respond well to ECT, whereas patients with "neurotic" depression do not. Consequently, ECT is the treatment of choice where drug therapy has failed in patients with "endogenous" depression, and this constitutes its main use in clinical practice.

There are patients in whom ECT is the appropriate initial treatment. Included are patients with recurrent depression and a history of unresponsiveness to drug therapy; patients with severe melancholic states, especially those accompanied by nihilistic or paranoid delusions; and patients in whom alteration of symptoms is imperative as quickly as possible, either due to suicidal tendencies or to excessive suffering.

Schizophrenic States

ECT is used infrequently for the treatment of schizophrenic states due to the proven benefits of phenothiazines and other drugs that inhibit dopaminergic transmission. ECT, however, may be indicated in acute schizophrenia associated with affective symptoms unresponsive to drug therapy. There is no indication for the administration of ECT to chronic schizophrenics (2).

Manic States

Currently, manic disorders are mostly managed with haloperidol, lithium, and phenothiazines; ECT is rarely indicated.

Administration Approach

All ECT devices produce electrical stimuli with a waveform, a frequency, and a duration that can be changed

through a wide range to evoke generalized seizures in virtually all individuals (18). The current state-of-the-art ECT device is one utilizing a brief pulse stimulus. Although originally used in the mid 1940s, recent use in clinical practice began with the development of the Multiple-Monitored Electroconvulsive Therapy Machine (MECTA) from Custom Systems Associates Inc. (Fig. 1) (19). This machine produces short pulses of current interrupted by longer periods of electrical inactivity, the electrical transmission lasting for only a fraction of total stimulus duration, thereby resulting in a decrease in the amount of electrical energy required to evoke a generalized seizure. This is in contrast to the old sine wave machines, where current amplitude varied continuously with stimulus duration. Stimulus frequency, pulse width, and total stimulus duration are adjustable variables on the MECTA machine. Typical settings are a pulse of 60 Hz of 0.75-msec duration, with a total stimulus time of 1.25 sec (20). A two-channel chart recorder for EEG and ECG allows monitoring of the presence and duration of seizure activity, as well as cardiac activity.

Electrode Placement

The electrical stimulus is attached to the patient's head by large plate or sponge electrodes to effect a low impedance pathway for the stimulus current (21). Electrodes may be fixed to the scalp by a headband or may be hand-held. Preparation of the electrode sites involves skin cleansing, mild abrading of the superficial skin layer, and application of electrode jelly or saline.

Most of the literature on ECT electrodes stresses the merits of different configurations of electrode

placement. Generally, with bilateral ECT, an electrode is placed over each cerebral hemisphere, whereas, with unilateral ECT both electrodes are placed over one hemisphere (22).

Seizure Characteristics

Electrically produced seizures are characterized by an initial very brief period of muscular contraction representing direct electrical stimulation of neural and muscular tissue, followed within 15 sec by a tonic phase persisting up to 20 sec that, in turn, is gradually replaced by a clonic phase. The latter phase is initially rapid and erratic, reaching a frequency of 2-3 Hz and lasting from a few brief seconds to over 1 min.

During electrically induced seizures, the EEG shows changes similar to those seen during spontaneous grand mal seizures, including a buildup of α and β rhythmic activity that may persist into the tonic phase, only to be masked by high-frequency muscle artifacts. Repetitive polyphasic spike and wave complexes that characterize the clonic phase are synchronous with clonic movements (23). A period of EEG suppression characterizes the end of the clonic phase.

The relationship between seizure duration and antidepressive effect is unclear, although it is accepted that generalized seizures are an essential part of treatment (23). Weiner considers a seizure of 25-60 sec to be adequate; a duration of less than 25 sec or greater than 60 sec generally indicates the need to adjust stimulus intensity (9).

Number of Treatments

The number of ECT treatments to be given is determined by the patient's clinical response, rather than by a fixed number of treatments. After apparent maximal clinical improvement (i.e., when successive treatments elicit no further beneficial effects) ECT should be discontinued (2).

Physiologic Effects of ECT

Cardiovascular System

Stimulation of the autonomic nervous system is the mechanism responsible for the cardiovascular changes that occur during ECT (Table 2). The disturbance consists of a parasympathetic-sympathetic sequence of events. The parasympathetic discharge occurs immediately after application of the current, with the sympathetic surge following within seconds (24,25). This initial sequence is followed by a similar but less dramatic sequence during the clonic phase of the sei-

Table 1. Physiologic Effects of Electroconvulsive Therapy

Cardiovascular effects
Immediate
Parasympathetic stimulation
Bradycardia
Hypotension
Late (after 1 min)
Sympathetic stimulation
Tachycardia
Hypertension
Dysrhythmias
↑ Myocardial oxygen consumption
Cerebral effects
↑ Cerebral oxygen consumption
↑ Cerebral blood flow
↑ Intracranial pressure
↑ Intraocular pressure
↑ Intra gastric pressure

zure that persists into the recovery period. Studies in both animals and humans have shown an increase in plasma catecholamines accompanying ECT (26,27).

In some patients the sequence described may result in an initial bradycardia or even asystole, resulting from the parasympathetic outflow, followed by tachycardia, dysrhythmia, and hypertension due to sympathetic stimulation. This, in combination with the increase in muscular tone and activity that accompanies ECT, results in a generalized increase in oxygen consumption, including myocardial oxygen consumption, which may result in myocardial ischemia or even infarction (28).

Cerebrovascular System

Alteration of cerebrovascular dynamics during ECT is striking. An initial brief period of cerebrovascular constriction concurrent with the passage of the electrical stimulus is observed followed by a sustained increase in cerebral blood flow of 1.5-7 times baseline flows. This increased flow is in part a response to increased systemic arterial pressure, but mainly represents a response to the increase in cerebral oxygen consumption that accompanies the seizure. This increased cerebral blood flow gives rise to a dramatic although transient increase in intracranial pressure that may be of particular concern in patients with intracranial mass lesions, vascular anomalies, or increased intracranial pressure from any etiology (29-32).

Miscellaneous

ECT produces significant elevation in intraocular pressure subsequent to the onset of the seizure (33).

Table 2. Contraindications to Electroconvulsive Therapy**Absolute**

Recent myocardial infarction
Recent cerebrovascular accident
Intracranial mass lesion

Relative

Angina pectoris
Congestive heart failure
Severe pulmonary disease
Severe osteoporosis
Major bone fractures
Glaucoma
Retinal detachment
Thrombophlebitis
Pregnancy

Elevated intragastric pressure is also an inevitable accompanying effect of the convulsion (34).

Contraindications

The literature affords little uniformity of opinion as to which conditions constitute relative or absolute contraindications to ECT (Table 2). The consensus, however, is that absolute contraindications include patients with intracranial space occupying lesions with or without changes in intracranial pressure (31) [although even this has been denied (32)], a cerebrovascular accident in the 3 months preceding the date of therapy, and increased intracranial pressure from any cause (35,36). Patients with a history of a myocardial infarction within the last 3 months or who have a documented aneurysm of a major vessel are also considered in most instances to be unsuitable for ECT (37), although ECT in the presence of a cerebral aneurysm (38) and during the acute phase of a myocardial infarction (39) has been reported.

Even greater diversity of opinion exists as to what constitutes relative contraindications to ECT. Those most frequently mentioned are angina pectoris, congestive heart failure, cardiac pacemakers, glaucoma, retinal detachment, severe osteoporosis, major bone fractures, thrombophlebitis, severe acute and chronic pulmonary disease, and pregnancy (34). On the other hand, successful ECT treatment in such patients have been reported (40-42).

In the final analysis, the decision to proceed with ECT in any patient should be predicated on analysis of the risks associated with treatment relative to the risks inherent in the progression of the unchecked psychiatric disease process and the risks inherent in long-term therapy with antidepressants. As such, many authorities consider ECT to be the most effective and safest form of treatment for severe depression, par-

ticularly in the elderly (43), where it is as safe as in the younger age groups (44).

Morbidity and Mortality of ECT

Modified ECT in association with skilled anesthetic management is safe and effective. The complication rate is on the order of one in 1700 treatments (5). Frequency and seriousness of the sequelae accompanying ECT are related to the underlying clinical status of the patient and the skill of the psychiatrist and anesthesiologist in successfully modifying the global effects of the seizure.

Vertebral and long bone fractures, which are feared complications of unmodified ECT, have not been reported in the last 10 years. Subjectively, the most common complaints of patients subjected to ECT have been the anxiety experienced at the approach of treatment, and muscle aches, headaches, and memory disturbances after treatment, the latter being the most troublesome side effect (34).

Damage to teeth, tongue, eyes, and cutaneous structures has been described when the patient was inadequately protected by the attending personnel. Even reports of cutaneous burns occurring when the patient's skin was allowed to touch a conductive surface during the passage of the current have appeared in the literature.

It should be emphasized that the seizure produced by ECT is often stated to produce complete retrograde amnesia, but this cannot be guaranteed. Indeed, some patients can recall after several years the frightening flash experienced before loss of consciousness during ECT (45).

Mortality directly attributable to ECT is very low; no such deaths were reported in four large studies in the last 15 years (46). In the 1940s the mortality from ECT was 0.06% (47). In the United Kingdom in the 5 years prior to 1953, 67 deaths were attributed to ECT. The majority of these deaths involved the cardiovascular or pulmonary systems: Two were attributed to cardiac arrest, three to pulmonary embolism, and at least two to anesthetic complications (48). Barker and Baker in 1959 reported a mortality rate for patients undergoing ECT to be one in 28,000 treatments (49).

Studies with smaller population samples, nevertheless, have reported deaths in association with ECT. Gerring and Shields reported one death in a series of 42 patients (50). Another series from the United States reported three deaths among of 1765 patients receiving ECT, and four deaths of 2594 patients were reported in the latest study from the United Kingdom (47). It is of note that the mortality rate in depressed patients is greater than in the age-corrected general

population, even when deaths from suicide are excluded; depressed patients given the benefit of treatment with ECT have a mortality rate similar to that of the age-corrected population (37).

Anesthetic Considerations

It is now standard practice for the anesthesiologist to be consulted about the anesthetic management of patients undergoing ECT. The approach to these patients must not be casual; the precepts underlying anesthetic management are the same as those for patients undergoing anesthesia for any operative procedure. In an effort to avoid or minimize the physiologic sequelae and attendant complications of ECT, a technique of modified ECT has evolved gradually, featuring the use of drugs to minimize the detrimental effects of ECT without the concomitant abolition of the essential beneficial effects.

Preanesthetic Management

All patients about to undergo ECT should receive a preanesthetic visit and evaluation from the anesthesiologist prior to each treatment. Due to the nature of the underlying disease process, most patients exhibit anxiety and fear, particularly before the first treatment. Some patients have delusional or suicidal tendencies and are uncommunicative. Discussion of the underlying psychiatric illness with the patient should be avoided (46). Although the anesthesiologist should be as reassuring as possible, however, the medico-legal requirements of explaining the risks and benefits of the anesthetic to the patient should still be observed. Obtaining informed consent is mandatory and should be obtained from relatives where appropriate.

The preoperative evaluation of all patients should include a detailed medical history and physical examination. Should past medical history not be available from the patient, the information should be obtained from old medical records, relatives, friends, and the attending psychiatrist. Because ECT is currently administered to patients with severe concomitant systemic disease, particular attention should be given to the evaluation of the patient's cardiopulmonary system and neurologic state. In the appropriate instances a more complete evaluation should be obtained by consultations with other medical specialists. Notes on the tendency to esophageal reflux, known allergies, previous anesthetic experiences, and concurrent medication that the patient may or may not be taking should also be made. Minimum preoperative laboratory data should include hemoglobin

and electrolyte levels within 48 hours of commencement of therapy, together with a recording of the patient's ECG. These studies should be repeated before subsequent treatments as clinically indicated. The routine use of a chest x-ray prior to ECT is not necessary (51) and has been criticized (52). Other laboratory data should be predicated on the clinical status of the patient.

The concomitant administration of psychotropic drugs is frequent in patients scheduled for ECT. A 1975 study of 425 patients for ECT showed all patients receiving some form of psychotropic medication, the tricyclic antidepressants and benzodiazepines being the most frequently administered and often in combination (53). Although the majority of such drugs have no effect on the course of the anesthetic, some do have implications for the anesthesiologist and should be noted. The monoamine oxidase inhibitors (MAOI) and the tricyclic antidepressants are the drugs most commonly implicated.

Tricyclic antidepressants, including imipramine and amitriptyline, are structurally related to phenothiazines and block the uptake of norepinephrine into presynaptic nerve terminals. Most of these drugs also have anticholinergic effects. The cardiotoxic effects of these drugs may be seen even in therapeutic doses leading to tachycardia and dysrhythmias (54-56). However, an antidysrhythmic effect of imipramine in cardiac patients has been demonstrated (57). The pressor response to direct acting sympathomimetic amines in patients receiving tricyclic antidepressants is increased manyfold, resulting in hyperthermia, hypertensive crises, and even death (58,59). It has been recommended, therefore, that tricyclic antidepressants be discontinued 2 wk prior to an anesthetic (60). This may not be possible or advisable in most psychiatric patients, however, and concurrent therapy with tricyclic antidepressants should not in and of itself be a contraindication to anesthesia for ECT. Spiss et al. concluded that chronic imipramine therapy, as opposed to acute administration, did not alter arrhythmogenicity and adrenergic responsiveness to epinephrine nor norepinephrine, at least in dogs (61). A possible explanation for this is that compensatory mechanisms at the adrenergic nerve terminal during chronic therapy revert the initial hypersensitivity to a normal level of sensitivity to catecholamines. Should an hypertensive crisis develop, prompt treatment should be instituted to alleviate the problem.

Monoamine oxidase (MAO) inhibitors exert their effects through their ability to inhibit the MAO that is essential in the intraneuronal metabolism of sympathomimetic amines, as well as the metabolism of many other drugs at various sites in the body. The

ability of drugs to block MAO accounts for both their effectiveness in the treatment of severe depression and their interactions with anesthetic agents. Monoamine oxidase inhibitors are infamous for their ability to interact with sympathomimetic amines, notably the indirectly acting sympathomimetic amines, to precipitate a hypertensive crisis (61-64). These hypertensive responses can be eliminated by withdrawal of the MAO inhibitors 2 wk prior to anesthesia. As with the tricyclic antidepressants this may not be practical nor desirable in psychiatric patients, especially those needing ECT, and the anesthesiologist, thus, should be prepared to treat any crisis that may arise when anesthesia must be given for ECT in patients maintained on MAO inhibitors. Due to the increased risks that are associated with anesthesia and ECT in patients taking MAO inhibitors, some psychiatrists believe that ECT should not be performed (3). El-Ganzouri et al., however, suggest that discontinuation of chronic MAOI therapy prior to anesthesia is not necessary because ECT in their patients was not associated with complications attributable to MAO inhibitor therapy (65).

A major consideration for the anesthesiologist concerns drug interaction of both tricyclic antidepressants and MAO inhibitors with barbiturates. Both groups of drugs augment the effects of barbiturates, increasing sleep time, duration of anesthesia, and lethality (66,67). Lower barbiturate dosages should be used in patients concomitantly taking tricyclic antidepressants or MAOI.

Lithium carbonate has recently been introduced as very useful for the treatment of recurrent depression (68). Although it is regarded as safe for patients receiving lithium to undergo ECT (69,70), when serum lithium levels are outside the therapeutic range, even without overt signs of toxicity, interaction with barbiturate anesthesia may lead to prolonged recovery times (71,72). As lithium tends to act as an imperfect sodium ion, interaction with neuromuscular blockers in such patients has also been documented. The action of depolarizing neuromuscular blockers in patients receiving lithium is markedly prolonged, as is the action of the nondepolarizing agent pancuronium. However, no prolongation of neuromuscular block following gallamine nor *d*-tubocurarine has been demonstrated (73-75).

Rauwolfia alkaloids, although rarely if ever used in the treatment of depression now, are still used in the treatment of hypertension and have been reported to have serious consequences in patients undergoing ECT. These drugs produce their effects through intraneuronal catecholamine depletion (76) and have been reported to produce apnea, profound hypoten-

sion, cardiac dysrhythmias, and even death in patients receiving concomitant ECT therapy. All patients receiving rauwolfia alkaloids, therefore, should have a 2-wk treatment-free period prior to anesthesia and ECT (77-81).

The immediate preanesthetic preparation of the patients, as for any anesthetic, must include a period of fasting for at least 6 hr. This may seem simple, but many of these patients are extremely unreliable and occasionally uncooperative. Careful supervision of the patient is required to ensure that fasting does occur. Most psychiatrists schedule ECT treatments in the early morning in order to minimize the fasting period (46).

Preanesthetic medication with sedatives or narcotics is not required and may serve only to prolong the anesthetic recovery time. Reassurance from the psychiatric staff should be sufficient to allay most of the patient's fears regarding the upcoming treatment. Preoperative use of anticholinergic agents to reduce the excess vagal stimulation of the heart and decrease secretions associated with ECT has become routine (3,4,53). Some authors suggest that the optimal route of administration is the intramuscular route 30-45 min prior to anesthesia (82). Administration via the intravenous route at the time of induction of anesthesia, however, has been demonstrated to be as effective as the intramuscular route in attenuating vagal responses and avoiding the attendant side effect of a dry mouth (83). Although atropine has been the most frequently administered anticholinergic drug, its use in ECT has recently been compared with glycopyrrolate. When administered intravenously at induction of anesthesia they were found to afford equal protection against the vagotonic cardiac effects of ECT and in their antisialagogue effects. However, atropine was associated with a greater increase in heart rate than glycopyrrolate and the latter, thus, was recommended over atropine whenever an anticholinergic agent is deemed necessary (84).

The absolute necessity of anticholinergic pretreatment for ECT has been criticized as being potentially harmful to the patient and ineffective in conveying any particular advantage to the conduction of the anesthetic. A report of 6000 ECT treatments revealed no incidence of severe bradycardia or difficulty with airway secretions when performed without atropine pretreatment (85). Furthermore, in a controlled study, Wyant and MacDonald could find no benefit to the patient of pretreatment with anticholinergic medication (86).

Patients receiving tricyclic antidepressants, which possess central and peripheral anticholinergic activity, have an additive response with preanesthetically

administered centrally acting anticholinergic agents. The combined administration of the two types of drugs have been reported to cause delirium and confusion in the postanesthetic period (87,88). Anticholinergic agents that do not cross the blood-brain barrier, such as glycopyrrolate, therefore, are recommended in patients taking tricyclic antidepressants, should an anticholinergic drug be needed (89).

Pretreatment with anticholinergic agents, therefore, cannot be said to be mandatory for the conduction of ECT and the decision to use these agents should be made on an individual basis. Should these agents be considered necessary it seems that glycopyrrolate has certain advantages over atropine.

Anesthetic Management

Administration of a general anesthetic for ECT treatment must be performed only where equipment for the support and the resuscitation of the unconscious patient is immediately available, together with facilities for the treatment of complications. All patients undergoing ECT must have ready intravenous access (either an in situ heparin lock intravenous canula or an ongoing intravenous infusion) for drug administration and must have monitoring of ECG and blood pressure as minimum requirements.

Preoxygenation of patients is not mandatory, provided that ventilation is routinely assisted as necessary during anesthesia for ECT (90). Should the application of a mask be distressing to the patient, therefore, preoxygenation can be safely omitted. Anesthetic requirements for successful ECT are fourfold:

1. Rapid induction
2. Attenuation of the physiologic effects of ECT
3. Rapid recovery after the seizure
4. Minimization of any antagonistic effects on seizure activity by anesthetic agents

Induction Agents

Most of the currently available agents for the induction of general anesthesia have been used at some time or another for induction of anesthesia for ECT. Methohexital is now the most commonly used of the induction agents.

Methohexital (Brevital) is a barbiturate with a rapid onset and a short duration of action that decreases the duration of and raises the threshold to electrically induced seizures (91,92), the latter perhaps leading to undertreatment (93). Miller et al. found an inverse relationship between the dose of methohexital used and the seizure duration. Whether or not manipula-

tion of the dose used can influence seizure activity in any individual patient was undetermined. Increased sensitivity to the hypnotic and sedative effects of induction agents has been reported in patients with psychotic depressive illnesses (53,94). Pain on injection of methohexital is not an infrequent occurrence, and a starting dose of 0.75 mg/kg has been recommended by several authors with adjustments as required, for subsequent treatments (46,95).

McCleave and Blakemore, in one of the few controlled studies comparing induction agents for ECT anesthesia, compared methohexital and thiopental and found no difference between the two agents for induction time or awakening time (53). On the other hand, two comparative studies have appeared in the psychiatric literature showing that anesthesia for ECT was slower in onset and recovery was delayed longer with thiopental than with methohexital (90,96). The technique of administration of the two drugs, however, was markedly different and did not correspond with current anesthetic practice. As such, the results must be treated with caution. The incidence of postictal ECG abnormalities also has been reported to be greater with thiopental than with methohexital, especially in patients with preexisting heart disease (90,95,96). The high incidence of cardiac dysrhythmias in these studies may have been a result of hypoxia, because patients were only ventilated postictally when arterial oxygenation reached hypoxic levels. McCleave and Blakemore reported no increase in cardiac complications when their patients were supported with controlled ventilation until recovery of spontaneous ventilation was established (53). It seems that at best thiopental offers no advantage over methohexital as the anesthetic of choice for ECT.

Diazepam has been recommended as the anesthetic of choice for ECT in several reports (97,98). Diazepam increases the seizure threshold (99) and shortens seizure duration (100). A comparative study with methohexital showed significantly greater postictal ECG abnormalities and recollection of frightening apnea with diazepam anesthesia (101). However, none of these complications were reported in over 700 ECT inductions with diazepam by Wehlage (102). These facts, together with a reportedly longer induction period and delayed recovery (53), should restrict the use of diazepam in ECT to patients in whom barbiturates are contraindicated.

Ketamine and etomidate also have been used as anesthetic agents in ECT. Although ketamine has been reported to have cerebral anticonvulsant properties, at least in animals (103), ketamine also increases duration of electrically induced seizures in both the animals and humans (93). Although claimed to be su-

perior to other agents (104), a comparative study of ketamine with methohexital showed the latter to be better, ketamine being associated with a significantly slower onset of anesthesia, delayed recovery, and a greater incidence of nausea and ataxia postanesthetically (105). Emergence phenomena, associated with non-ECT use of ketamine, is rare when it is used in ECT and probably is due to the effects of the treatment (93,105). To date, etomidate has not been compared with methohexital for ECT anesthesia. However, two studies on its use in ECT patients found it to be satisfactory although a significant number of patients experienced pain on injection of the drug (106,107). As with diazepam, the use of ketamine and etomidate in ECT probably should be restricted to patients in whom barbiturate administration would be considered inadvisable.

Of the above mentioned induction agents, the development of acute tolerance on repeated administrations has been described for thiopental and ketamine (108,109). However, the clinical significance of this phenomenon during the administration of anesthesia for ECT remains to be determined.

Muscle Relaxants

Succinylcholine is now universally used as the muscle relaxant of choice in ameliorating the violence of muscle contraction associated with ECT. Its use in ECT, thereby, has virtually eliminated the risks of fractures, notably vertebral fractures, which were of major concern with unmodified ECT therapy. An undesirable effect of succinylcholine is impairment of the psychiatrist's ability to determine the extent of the patient's seizure or if, indeed, any seizure occurred at all. The modern MECTA ECT machine eliminates this problem by monitoring EEG activity, thereby allowing an accurate estimation of the induced seizure. A suitable alternative monitor of seizure activity in modified ECT has involved vascular isolation of an arm using an arterial tourniquet prior to administration of succinylcholine. Fink et al. have shown that arm movements under such circumstances correlate positively with EEG monitoring of seizure activity (110).

The optimum dose of succinylcholine in ECT has come under some scrutiny. Pitts et al. recommend 0.5 mg/kg, noting that less than that offered little protection against seizure severity and greater than 0.5 mg/kg increased the duration of apnea (111). It also has been shown that the dose of succinylcholine used had an inverse relationship with the duration of seizure activity, either as a result of altered peripheral input to the CNS from succinylcholine use, or from

alteration in blood-brain barrier permeability to succinylcholine during the seizure (112). Thus, until the relationship between duration of seizure and efficacy of ECT is clarified, succinylcholine dose should be modified on an individual basis to correspond with clinical results and to minimize effects on seizure duration.

Both succinylcholine administration and severe muscular exercise have been reported to produce small increases in serum potassium levels (113,114). Bali showed elevations in serum potassium levels to be significantly greater in patients receiving anesthesia-succinylcholine-ECT than in a similar group without the ECT (115). The increase in serum potassium levels has been reported to be primarily in patients receiving methohexital-succinylcholine-ECT, with patients having thiopental-succinylcholine-ECT showing no increase (116). Pilditch et al. and Bali showed significant elevations with both types of anesthetic (115,117), whereas, McCleave et al. could show no significant increase when lower doses of succinylcholine were used (53). It should be noted that although the elevations in serum potassium were statistically significant, no dangerous levels of potassium were noted and all rises occurred within the first minute of ECT therapy. However, the increase may be clinically significant in patients predisposed to hyperkalemic responses to intravenous succinylcholine.

Muscle pains after intravenous injection of succinylcholine have been known since 1952, particularly in ambulatory patients (118,119). However, the incidence of muscle pains after anesthesia for modified ECT appears to be very low, with one study reporting an incidence of 2%. No relationship between the incidence of pains and induction agent used could be demonstrated (53).

The current practice of attenuation of the adverse effects of succinylcholine administration with prior administration of a nondepolarizing neuromuscular blocker has not been investigated in patients undergoing ECT. Miller et al. showed that small, nonparalyzing doses of gallamine or *d*-tubocurarine are effective in this regard without affecting the type or magnitude of neuromuscular block produced by succinylcholine (120). The effects of nondepolarizing neuromuscular blockers on the duration of seizure activity and effectiveness of ECT has not been reported.

Where succinylcholine is contraindicated (e.g., patients with pseudocholinesterase deficiency), administration of ECT using thiopental and gallamine has been reported (121) without apparent adverse effects.

The use of the newer, short-acting nondepolarizing neuromuscular blocking agents atracurium and vecuronium in such circumstances has not been reported but appears promising.

Modification of Sympathetic Response to ECT

Sympathetic stimulation exhibited by hypertension and dysrhythmias are common sequelae of ECT therapy (34). These responses frequently are severe and potentially catastrophic in patients with ischemic cardiovascular disease, vascular aneurysms, and hypertension, the latter exhibiting a greater response than normotensive patients (25,26,122). Various agents have been used in the attenuation of these responses. Sodium nitroprusside pretreatment significantly attenuates the hypertensive and rate-pressure response of ECT (123), but may be associated with persistent hypotension after ECT (124). Clonidine given orally 2 hr before ECT significantly attenuates heart rate and rate pressure response to ECT (123). Application of nitroglycerin ointment 45 min before treatment also significantly attenuates ECT-induced hypertension (125). Propranolol and lidocaine pretreatment is ineffective in attenuating the hypertensive response (123), although propranolol in combination with hydralazine was effective in one reported case (38).

Attenuation of ventricular dysrhythmias associated with ECT has been effected by pretreatment with propranolol (126) and pretreatment with a combination of propranolol and atropine (127). Pretreatment with propranolol, however, has been implicated with one case of asystole associated with ECT (128). Use of lidocaine in this manner is effective in attenuating dysrhythmias associated with ECT (129), but shortens electrically induced seizure activity (130) and has been said to prevent the initiation of a seizure (131).

Postanesthetic Considerations

The vast majority of patients undergoing ECT are ambulatory and are expected to resume their usual activity posttreatment. The immediate period after ECT has been reported to be a high risk time (49). Thus, recovery from the anesthetic should be closely monitored by the anesthesiologist or other qualified staff with readily available equipment for treatment of any emergency. No patient should be discharged until fully recovered from the anesthetic.

The postseizure phase occasionally is accompanied by varying degrees of agitation, confusion and, very rarely, violent behavior. This is most frequent in alcoholic, manic, or paranoid patients; once it occurs, it tends to be recurrent after each subsequent treat-

ment, irrespective of improvement in mental state (82). Avoidance of excessive stimulation in the immediate postictal phase and reassurance from the attending staff may minimize the incidence of postseizure agitation. Severe agitation can be attenuated by premedication with diazepam or haloperidol (97), but the effectiveness of the ECT may be diminished. An alternate method of control of agitation advocated by Dell'Aria et al. is administration of intravenous diazepam or small doses of thiopental immediately after the seizure (82).

Conclusion

The effectiveness of ECT depends on cooperation between the anesthesiologist and psychiatrist. Although the anesthetic period in ECT is brief, an understanding of the effects that anesthetic agents may have on seizure activity, an essential element in ECT therapy, is a prerequisite in the administration of an anesthetic for maximal patient benefit.

We have described the current knowledge on the psychologic and physiologic effects of ECT, interaction between anesthetic drugs and ECT requirements, and considerations for the conduct of an anesthetic for ECT.

References

1. Fraser MJ, ed. ECT—a clinical guide. Chichester and Toronto: Wiley Medical Publications, 1982:52-7.
2. Kendall RE. The present status of ECT. *Br J Psychiatry* 1981;139:265-83.
3. Pippard J, Egan L. Electroconvulsive treatment in Great Britain. *Br J Psychiatry* 1981;139:563-68.
4. Asnis GM, Fink M, Saferstein S. ECT in metropolitan New York hospitals. A survey of practice. *Am J Psychiatry* 1978;135:479-82.
5. Holden C. A guarded endorsement for electroshock therapy. *Science* 1985;228:1510-11.
6. Hoch PH. Clinical and biological interrelations between schizophrenia and epilepsy. *Am J Psychiatry* 1943;99:507-12.
7. Meduna L. General discussion of the cardiozole therapy. *Am J Psychiatry* 1938;94:40-50.
8. Bini L. Experimental research on epileptic attacks induced by the electric current. *Am J Psychiatry* 1938;94:172-4.
9. Weiner RD. The psychiatric use of electrically induced seizures. *Am J Psychiatry* 1979;136:1507-17.
10. Bennett AE. Prevention of traumatic complications in convulsive shock therapy by curare. *JAMA* 1940;114:322-5.
11. Bellett S, Kerschbaum A, Furst W. Electrocardiography during electric shock treatment of mental disorders. *Am J Med Sci* 1941;201:167-70.
12. Kolb L, Vogel V. Electroconvulsive treatment. *Am J Psychiatry* 1941;99:221-4.
13. Altschute MD, Sulzbach WM, Tolloston KJ. Significance of

- change in ECG after electric induced convulsions in man. *Arch Neurol and Psycho* 1947;58:316-20.
14. Hughenard P, Bone A. Un nouvel ortho-curare francais de synthese le 3697 a r p. Raport à la Soc d'Anesth de Paris, scande du, 7, 1948.
 15. Holmberg AG, Thesleff S. Succinylkolin jodid som muskelavslappande medel via elektroshock behandling. *S Nor Med* 1951;46:1567-70.
 16. Friedman E. Monograph supplement. Diseases of the Nervous System 1959;20:121-4.
 17. Valentine M, Keddle KMG, Dunne D. Comparison techniques in electroconvulsive therapy. *Br J Psychiatry* 1968;114:989-94.
 18. Davies RK, Detre TP, Egger MD, Tucker GJ, Wyman RJ. Electroconvulsive instruments. Should they be reevaluated? *Arch Gen Psychiatry* 1971;25:97-9.
 19. Fling J, Moulton CH. Electrical design considerations for ECT apparatus. *Convulsive therapy bulletin with tardive dyskinesia notes* 1976;1:37-38.
 20. Weiner RD. ECT and seizure threshold. *Biol Psychiatry* 1980;15:225-41.
 21. Weiner RD. ECT, some practical considerations concerning electrodes. *N C J Ment Health* 1979;8:41-7.
 22. Salzman C. Electroconvulsive therapy. In: Shader RI, ed. *Manual of psychiatric therapeutics*. Boston: Little Brown & Co., 1975.
 23. Ottoson JO. Seizure characteristics and therapeutic efficacy in electroconvulsive therapy: an analysis of the antidepressive efficiency of grand mal and lidocaine modified seizures. *J Nerv Ment Dis* 1962;135:239-51.
 24. Perrin GM. Cardiovascular aspects of electric shock therapy. *Acta Psychiatry Scand* 1961;36:1-45.
 25. Anton AH, Uy DS, Redderson CL. Autonomic blockade and the cardiovascular and catecholamine response to electroshock. *Anesth Analg* 1977;56:46-54.
 26. Jones RM, Waterland JW, Williams JP, Pearce AC. Cardiovascular and catecholamine responses to ECT in untreated hypertensives compared with normotensives. *Br J Anaesth* 1983;55:908P.
 27. Jones RM, Knight PR. Cardiovascular and hormonal responses to ECT. *Anaesthesia* 1981;36:795-99.
 28. Gaines GY, Giesecke AH. Hypotension during non-cardiac anesthesia in the cardiac patient. In: Brown BR, ed. *Contemporary anesthesia*, Vol. 2. Philadelphia: F. A. Davis & Co., 1980:101-9.
 29. Brodersen P, Paulson OB, Bolwig TG, Rogon AE, Rafaelson OJ, Lassen NA. Cerebral hyperemia in electrically induced epileptic seizures. *Arch Neurol* 1973;28:334-8.
 30. Loret-Doust JW, Raschka LB. Enduring effects of modified ECT on cerebral circulation in man. *Psychiatr Clin North Am* 1975;8:293-301.
 31. Maltbie AA, Wingfield RS, Volow MR, Weiner RD, Sullivan JL, Cavenar JO. Electroconvulsive therapy in the presence of a brain tumor. *J Nerv Ment Dis* 1980;168:400-5.
 32. Dressler DM, Folk J. The treatment of depression with ECT in the presence of a brain tumor. *Am J Psychiatry* 1975;132:1320-1.
 33. Epstein HM, Fagman W, Bruce DL, Abram A. Intraocular pressure changes during anesthesia for electroshock therapy. *Anesth Analg* 1975;54:479-81.
 34. Hurwitz TD. Electroconvulsive therapy: a review. *Compr Psychiatry* 1974;15:303-14.
 35. Moore MT. Electrocerebral shock therapy: a reconsideration of former contraindications. *Arch Neurol Psychiatry* 1947;57:693-711.
 36. Kalinowsky LB, Hippus H, eds. *Convulsive and other somatic treatments in psychiatry*. New York: Grune & Stratton, 1969:222-7.
 37. Avery D, Winokur G. Mortality in depressed patients treated with electroconvulsive therapy and antidepressants. *Arch Gen Psychiatry* 1976;33:1029-37.
 38. Husum B, Vester-Andersen T, Buchmann G, Bolwig TG. Electroconvulsive therapy and intracranial aneurysm. *Anaesthesia* 1983;38:1205-7.
 39. Karliner W. Cardiovascular disease and ECT. *Psychosom Med* 1978;19:238-41.
 40. Abiuso P, Dunkelman R, Proper M. Electroconvulsive therapy in patients with pacemakers. *JAMA* 1978;240:2459-60.
 41. Jauhar P, Weller M, Hirsch SR. Electroconvulsive therapy for patient with cardiac pacemaker. *Br Med J* 1979;1:90-1.
 42. Levine R, Frost EAM. Arterial blood gas analyses during electroconvulsive therapy in a parturient. *Anesth Analg* 1975;54:203-5.
 43. Rossman I. The role of ECT in the treatment of depression in the elderly. *J Am Geriatr Assoc* 1982;30:710-2.
 44. Mielke DH, Winstead DK, Goethe JW, Schwartz BD. Multiple-monitored electroconvulsive therapy: safety and efficacy in elderly depressed patients. *J Am Psychiatry Soc* 1984;32:180-2.
 45. Gomez J. Subjective side effects of ECT. *Br J Psychiatry* 1975;127:609-11.
 46. Rich CL, Smith NT. Anaesthesia for electroconvulsive therapy: a psychiatric viewpoint. *Can Anaesth Soc J* 1981;28:153-7.
 47. Marks RJ. Electroconvulsive therapy: physiological and anaesthetic considerations. *Can Anaesth Soc J* 1984;31:541-8.
 48. MacLay WS. Death due to treatment. *Proc R Soc Med* 1953;46:13-20.
 49. Barker JC, Baker AA. Deaths associated with electroplexy. *J Ment Sci* 1959;105:339-48.
 50. Gerring JP, Shields HM. The identification and management of patients with a high risk for cardiac arrhythmias during modified ECT. *J Clin Psychiatry* 1982;42:140-3.
 51. Abramczuk JA, Rose NM. Pre-anaesthetic assessment and the prevention of post-ECT morbidity. *Br J Psychiatry* 1979;134:582-7.
 52. Rees AM, Roberts CJ, Bligh AS, et al. Routine preoperative chest radiography in non-cardiopulmonary surgery. *Br Med J* 1976;1:1333-5.
 53. McCleave DJ, Blakemore WB. Anaesthesia for electroconvulsive therapy. *Anaesth and Intens Care* 1975;3:250-6.
 54. Burrows GC, Vohra J, Hunt D, Sloman JG, Scoggins BA, Davies B. Cardiac effects of different tricyclic antidepressant drugs. *Br J Psychiatry* 1976;129:335-41.
 55. Williams RB, Sherter C. Cardiac complications of tricyclic antidepressant therapy. *Ann Intern Med* 1971;74:395-8.
 56. Veith RC, Ruskind MA, Caldwell JH, Barns RF, Gumbrecht G, Ritcher JL. Cardiovascular effects of tricyclic antidepressants in depressed patients with chronic heart disease. *N Engl J Med* 1982;306:954-9.
 57. Giardina EGV, Louie M, Bigger T, Brem R, Alchevsky D. Antiarrhythmic plasma concentration range of imipramine against ventricular premature depolarizations. *Clin Pharmacol Ther* 1983;34:284-9.
 58. Boakes AJ, Laurence DR, Teoh PC. Interaction between sympathomimetic amines and antidepressant agents in man. *Br Med J* 1973;1:311-5.
 59. Svedmyr N. The influence of a tricyclic antidepressive agent (protriptyline) on some of the circulatory effects of noradrenaline and adrenaline in man. *Life Sci* 1968;7:77-81.
 60. Janowsky EC, Risch SC, Janowsky DS. Psychotropic agents.

- In: Smith NT, Miller RD, Corbasco AN, eds. Drug interactions in anesthesia. Philadelphia: Lea & Febiger, 1981:177-95.
61. Spiss CK, Smith CM, Maze M. Halothane-epinephrine arrhythmias and adrenergic responsiveness after chronic imipramine administration in dogs. *Anesth Analg* 1984;63:825-8.
 62. Perks ER. Monoamine oxidase inhibitors. *Anaesthesia* 1964;19:376-86.
 63. Jenkins LC, Graves HB. Potential hazards of psychoactive drugs in association with anaesthesia. *Can Anaesth Soc J* 1965;12:121-8.
 64. Schwartz AJ, Woollman H. Anesthetic considerations for patients on chronic drug therapy: L-Dopa, monoamine oxidase inhibitors, tricyclic antidepressants and propranolol. *Anesthesiology* 1976;44:98-111.
 65. El-Ganzouri AR, Ivankovich AD, Braverman B. Monoamine oxidase inhibitors: should they be discontinued preoperatively? *Anesth Analg* 1985;64:592-6.
 66. Dobkin AB. Potentiation of thiopental anesthesia by derivatives and analogues of phenothiazine. *Anesthesiology* 1960;21:292-6.
 67. Domino E, Sullivan TS, Luby ED. Barbiturate intoxication in a patient treated with a MAO inhibitor. *Am J Psychiatry* 1962;118:941-3.
 68. Davis JM, Janowsky DS, El-Yousef MK. The use of lithium in clinical psychiatry. *Psychiatr Annals* 1973;3:78-82.
 69. Schou M. Lithium in psychiatric therapy and prophylaxis. *J Psychiatr Res* 1968;6:67-9.
 70. Vlissides DN, Lee CR, Hill SE. Lithium, anaesthesia and ECT. *Br J Anaesth* 1979;51:574.
 71. Jephcott G, Kerry RJ. Lithium: an anaesthetic risk. *Br J Anaesth* 1974;46:389-90.
 72. Mannisto PT, Saarnivaara L. Effect of lithium and rubidium on the sleeping time caused by various intravenous anaesthetics in the mouse. *Br J Anaesth* 1976;48:185-90.
 73. Borden H, Clarke M, Katz H. The use of pancuronium bromide in patients receiving lithium carbonate. *Can Anaesth Soc J* 1974;21:79-82.
 74. Hill GE, Wong KC, Hodges MR. Potentiation of succinylcholine neuromuscular blockade by lithium carbonate. *Anesthesiology* 1976;44:439-42.
 75. Hill GE, Wong KC, Hodges MR. Lithium carbonate and neuromuscular blocking agents. *Anesthesiology* 1977;46:122-6.
 76. Alper MH, Flacke W, Krager O. Pharmacology of reserpine and its implications for anesthesia. *Anesthesiology* 1963;24:524-42.
 77. Foster MW Jr, Gayle RF Jr. Dangers in combining reserpine with electroconvulsive therapy. *JAMA* 1955;154:257-60.
 78. Bracha S, Hes JP. Death occurring during combined reserpine-electroshock therapy. *Am J Psychiatry* 1956;113:257.
 79. Coakley CS, Alpert S, Boling JS. Circulatory responses during anesthesia of patients on rauwolfia therapy. *JAMA* 1956;161:1143-4.
 80. Ziegler CH, Lovette JB. Operative complications after therapy with reserpine and reserpine compounds. *JAMA* 1961;176:916-9.
 81. Freeman DX. Critique of tranquilizing drugs, chlorpromazine and reserpine in neuropsychiatry. *N Engl J Med* 1956;255:877-83.
 82. Dell'Aria S, Karliner W. Anesthesiologic considerations in psychiatric convulsive therapy. *Behav Neuropsychiatry* 1975;6:6-17.
 83. Clement AJ. Atropine premedication for electric convulsion therapy. *Br Med J* 1962;1:228-9.
 84. Greenan J, Dewar M, Jones CJ. Intravenous glycopyrrolate and atropine at induction of anaesthesia: a comparison. *J R Soc Med* 1983;76:369-371.
 85. Vereeke G, Troch E. Atropine in ECT. *Anaesth Intens Care* 1982;10:166.
 86. Wyant GM, MacDonald WB. The role of atropine in electroconvulsive therapy. *Anaesth Intens Care* 1980;8:445-50.
 87. El Jousef MK, Janowsky DS, Davis JM, Sekerke HJ. Reversal of antiparkinsonian drug toxicity by physostigmine: a controlled study. *Am J Psychiatry* 1973;130:141-5.
 88. Milner G, Hills N. Adynamic ileus and nortriptyline. *Br Med J* 1966;1:841-2.
 89. Janowsky DS, Janowsky EC. Methscopolamine as a pre-anesthetic medication. *Can Anaesth Soc J* 1976;23:334-5.
 90. Woodruff RA Jr, Pitts FN, McClure JN. The drug modification of ECT. I. Methohexital, thiopental and preoxygenation. *Arch Gen Psychiatry* 1968;18:605-11.
 91. Ayd FJ. Methohexital (brevital): a new anesthetic for electroconvulsive therapy. *Dis Nerv Syst* 1961;22:388-90.
 92. Lann RJ, Savageau MM, Beatty WW, Gerst JW, Staton RD, Brumback RA. Anesthetics and electroconvulsive therapy seizure duration: implications for therapy from a rat model. *Biol Psychiatry* 1981;16:1163-75.
 93. Jones G, Callender K. Northwick park ECT trial. *Lancet* 1981;i:500-1.
 94. Shagass C, Schwartz M. Cerebral cortical reactivity in psychotic depressions. *Arch Gen Psychiatry* 1962;6:235-8.
 95. Witzum J, Baker M, Woodruff RA Jr, Pitts FN Jr. Electrotherapy: the effects of methohexital on EKG. *Dis Nerv Syst* 1970;31:193-5.
 96. Pitts FN Jr, Desmaris GM, Stewart W, Schaberg K. Induction of anesthesia with methohexital and thiopental in electroconvulsive therapy. *N Engl J Med* 1965;273:353-9.
 97. Gomez J, Dally P. Intravenous tranquilization with ECT. *Br J Psychiatry* 1975;127:604-6.
 98. Martin DJ, Kaelbling R. Diazepam modified electroconvulsive therapy. *Biol Psychiatry* 1971;3:129-39.
 99. Watson AC. Diazepam in convulsive therapy. In: Knight PF, Burgess CG, eds. *Diazepam in anaesthesia*. Bristol: J Wright & Sons, 1968:77-81.
 100. Stromgren LS, Dahl J, Fieldborg N. Factors affecting seizure duration and number of seizures applied in unilateral electroconvulsive therapy—anaesthetics and benzodiazepines. *Acta Psychiatr Scand* 1980;62:158-65.
 101. Allen RE, Pitts FN Jr. Drug modification of ECT: methohexital and diazepam. *Biol Psychiatry* 1979;14:69-76.
 102. Wehlage DF. *Conv Ther Bull* 1976;1:27.
 103. Eeder BS, Trapp LD, Troutman KC. Ketamine suppression of chemically induced convulsions in the two-day-old white leghorn cockerel. *Anesth Analg* 1980;59:406-9.
 104. Brewer CL, Davidson JRT, Hereward S. Ketamine: a safer anaesthetic for ECT. *Br J Psychiatry* 1972;120:679-80.
 105. McInnes EC, James NM. A comparison of ketamine and methohexital in electroconvulsive therapy. *Med J Aust* 1972;1:1031-2.
 106. Crispin A, Crommen AM. A progress in electroconvulsive therapy—the non-barbiturate anaesthetic drug etomidate. *Acta Psychiatry (Belg)* 1977;76:678-87.
 107. O'Carroll TM, Blogg CE, Hoinville EA, Savage TM. Etomidate in electroconvulsive therapy: a within patient comparison with alphaxalone/alphadalone. *Anaesthesia* 1977;32:868-72.
 108. Dundee JW, Price HL, Dripps RD. Acute tolerance to thiopentone in man. *Br J Anaesth* 1956;28:344-52.
 109. Slogoff S, Allen GW, Wessels JV, Cheney DH. Clinical ex-

- perience with subanesthetic ketamine. *Anesth Analg* 1974;53:354-8.
110. Fink M, Johnson M. Monitoring the duration of electroconvulsive therapy seizures. Cuff and EEG methods compared. *Arch Gen Psychiatry* 1982;39:1189-91.
111. Pitts FN, Woodruff RA, Craig AG, Rich CL. The drug modification of ECT II: succinylcholine dosage. *Arch Gen Psychiatry* 1968;19:595-8.
112. Miller AL, Faber RA, Hatch JP, Alexander HE. Factors affecting amnesia, seizure duration and efficacy in ECT. *Am J Psychiatry* 1985;142:692-6.
113. Paton WDM. Mode of action of neuromuscular blocking agents. *Br J Anaesth* 1956;28:470-4.
114. Kilburn KH. Muscular origin of elevated plasma potassium during exercise. *J Appl Physiol* 1966;21:675-8.
115. Bali IM. The effect of modified electroconvulsive therapy on plasma potassium concentration. *Br J Anaesth* 1975;47:398-401.
116. Haw ME. Variations in serum potassium during electroconvulsive therapy. *Br J Anaesth* 1972;44:707-11.
117. Pilditch FD, Baker AB. The effects of modified electroconvulsive therapy and four induction agent-relaxant regimens on serum potassium. *Anaesth Intens Care* 1974;2:142-6.
118. Bourne JG, Collier HOJ, Somers GF. Succinylcholine (succinylcholine) muscle-relaxant of short action. *Lancet* 1952;i:1225-9.
119. Churchill-Davidson HC. Suxamethonium and muscle pains. *Br Med J* 1954;1:74-5.
120. Miller RD, Way WL. The interaction between succinylcholine and subparalyzing doses of *d*-tubocurarine and gallamine in man. *Anesthesiology* 1971;35:567-71.
121. Brunton CR, Free CW. ECT without suxamethonium. *Anaesth Intens Care* 1983;11:177-8.
122. Jones RM. ECT for patients with hypertensive heart disease. *Am J Psychiatry* 1983;140:139.
123. Liu WS, Petty WC, Jeppsen A, Wade EJ, Pace NL. Attenuation of hemodynamic and hormonal responses to ECT with propranolol, xylocaine, sodium nitroprusside or clonidine. *Anesth Analg* 1984;63:244.
124. Ciraulo D, Lind L, Salzman C, Pilon R, Elkins R. Sodium nitroprusside treatment of ECT-induced blood pressure elevations. *Am J Psychiatry* 1978;135:1105-6.
125. Lee JT, Erbguth PH, Stevens WC, Sack RL. Modification of electroconvulsive therapy induced hypertension with nitroglycerin ointment. *Anesthesiology* 1985;62:793-6.
126. Weiner RD, Henschen GM, Dellasega M, Baker JS. Propranolol treatment of an ECT-related ventricular arrhythmia. *Am J Psychiatry* 1979;136:1594-5.
127. London SW, Glass DD. Prevention of electroconvulsive therapy-induced dysrhythmias with atropine and propranolol. *Anesthesiology* 1985;62:819-22.
128. Wulfson HD, Askanazi J, Finck AD. Propranolol prior to ECT associated with asystole. *Anesthesiology* 1984;60:255-6.
129. Usubiaga JE, Gustafson W, Moya F, Goldstein B. The effect of intravenous lignocaine on cardiac arrhythmias during electroconvulsive therapy. *Br J Anaesth* 1967;39:867-75.
130. Wikinski JA, Usubiaga JE, Morales RL, Torrieri A, Usubiaga LE. Mechanisms of convulsions elicited by local anesthetic agents. I. Local anesthetic depression of electrically-induced seizures in man. *Anesth Analg* 1970;49:504-10.
131. Hood DD, Mecca RS. Failure to initiate electroconvulsive seizures in a patient pretreated with lidocaine. *Anesthesiology* 1983;58:379-81.

Clinical Reports

Intrathecal Morphine in a Parturient with Cystic Fibrosis

Nicholas H. Hyde, MD, and Deborah M. Harrison, MB, ChB

Cystic fibrosis (CF), an autosomal recessive disease primarily characterized by abnormally thick secretions from mucous glands and pancreatic insufficiency, occurs predominantly in whites with a frequency of 1 in 1600 births (1). The main clinical features of CF are related to chronic, diffuse, obstructive pulmonary process and dysfunction of the pancreas. Morbidity and mortality in cystic fibrosis are primarily due to extensive recurrent pulmonary infections that lead to respiratory failure. Cor pulmonale is a common late complication.

Until recently, children with CF did not reach reproductive age. However, with improved management, antibiotic therapy, and enzyme supplements, more women with CF are reaching adulthood (2), and pregnancy is becoming more common. An optimal plan of obstetric analgesia has yet to be clearly defined. We report here a case of labor and delivery in a patient with CF, managed with intrathecal morphine analgesia.

Case Report

A 21-yr-old primigravida with a history of cystic fibrosis since early childhood was admitted to the obstetric unit at 37 weeks gestation. The course of her cystic fibrosis had been one of frequent respiratory infections and pancreatic insufficiency, which were treated with intermittent antibiotics, postural drainage performed daily by her husband, and continuous pancreatic enzyme replacement and vitamins.

A therapeutic abortion had been advocated in early pregnancy but was refused by the patient. Except for her need for chronic respiratory care, the patient con-

tinued to do well as her pregnancy progressed, although she had minimal weight gain.

Spontaneous labor occurred at 37 weeks gestation. On physical examination in the labor unit she was a pale, cachectic, 54-kg, 160-cm white female, somewhat dyspneic, with a chronic and productive cough. Vital signs were within normal limits except for a respiratory rate of 28 breaths/min. She had difficulty clearing her bronchial secretions. The supine position exacerbated her respiratory problems. Auscultation revealed diffuse rales and rhonchi throughout both lungs, with a prominent pulmonary second sound. The cervix was dilated to 3 cm. There was marked clubbing of the fingers and toes.

Laboratory studies on admission revealed a hemoglobin of 11.6 g/dl and a hematocrit of 35%. All other laboratory studies were within normal limits. Arterial blood gas tensions while breathing room air were PaCO_2 , 37 mm Hg, PaO_2 , 60 mm Hg, and pH 7.41. Pulmonary function tests showed her FEV_1 to be 0.97 (32% of predicted), her FVC to be 1.84 (49% of predicted), and her FEV_1/FVC to be 53 (81% of predicted). The electrocardiogram was normal. Fetal monitoring revealed a reactive tracing with no decelerations.

Nasal oxygen was started and labor progressed. Her chronic productive cough and dyspnea was somewhat relieved by cold steam mask (40% oxygen) and sitting upright. The patient requested analgesia when the cervix achieved 4 cm dilation. A lumbar puncture was performed with the patient in the sitting position at the L3-4 interspace using a 26-gauge spinal needle. Morphine sulfate, 1 mg in 1 ml of normal saline without preservatives, was injected intrathecally. The procedure required approximately 5 min and was well-tolerated by the patient. The patient returned to head-up position at approximately 60° angle after completion of procedure.

The onset of analgesia occurred within 20 min, and within 45 min the patient was no longer aware of uterine contractions. Analgesia was not associated with

Received from the Department of Anesthesiology, Yale University School of Medicine, New Haven, Connecticut. Accepted for publication July 1, 1986.

Address correspondence to Dr. Harrison, Department of Anesthesiology, Yale University School of Medicine, 333 Cedar Street, New Haven, CT 06510.

changes in blood pressure, pulse rate, sensory, or motor function. There were no changes in uterine activity or fetal heart rate.

Five hours after the morphine administration, the patient complained of rectal discomfort and, on examination, was found to be fully dilated. Pudendal block with 1% lidocaine was administered for delivery. Six hours after narcotic administration, a healthy baby girl was delivered with low forceps. Apgar scores for the infant were 9 at both 1 and 5 min. After delivery, the patient was transferred to the intensive care unit for 24 hr for respiratory monitoring. No supplemental analgesia for the episiotomy was required for 24 hr after delivery. The patient complained of mild pruritus that responded promptly to 0.08 mg of intravenous naloxone. A total of three doses was administered. She had no headaches, urinary retention, respiratory depression, or other sequelae and was discharged after 7 days.

Discussion

Although case reports of pregnancy in patients with CF are no longer unique (2,3), anesthetic management seems to concentrate on avoidance of certain drugs and procedures rather than on an optimal technique.

We postulated that intrathecal morphine could provide adequate analgesia in a parturient with cystic fibrosis with significant pulmonary disease (i.e., dyspnea, chronic productive cough, inability to clear secretion while supine, and underlying pulmonary hypertension) while avoiding some of the potential complications associated with other anesthetic techniques.

We did not select epidural anesthesia by means of local anesthetic agents for three reasons. Because of the chronic cough and orthopnea, both the required time and required positioning for an epidural anesthetic would cause additional discomfort for the patient. Second, the patient might be unable to handle the intravenous fluids that are normally needed for continuous lumbar epidural anesthesia. Third, the possibility of sympathetic blockade with resultant hypotension would necessitate both intravenous fluids and the supine position. These two maneuvers would make the patient's breathing worse and fluid management more complex.

In this patient, subarachnoid injection of morphine resulted in excellent analgesia without the aforementioned potential problems. Epidural narcotics have been reported to provide analgesia when used in labor (4), and the high dose of morphine required epidurally is associated with an increased incidence of side

effects (pruritus, nausea, potential for respiratory depression). Intrathecal morphine, in a dose of 1-2 mg, has been reported to be effective in providing adequate analgesia during the first stage of labor, although supplemental analgesia is required for delivery (5).

The intrathecal route for narcotics provides several advantages. First, and especially germane in this patient, subarachnoid narcotics can be rapidly injected in the sitting or semi-upright position. Second, fluid loading is not needed because of the absence of sympathetic blockade. Yaksh et al. have shown that analgesia produced by intrathecal injection of morphine has no detectable effect on the initiation and progress of labor in rats (6). Unlike systemic narcotics, with their potential for neonatal and maternal depression, morphine, when injected intrathecally, uses much smaller amounts to achieve the desired effect. This form of analgesia is not associated with any changes in pinprick sensation or motor power, arterial blood pressure, heart rate, or infant morbidity (5). Finally, should any untoward reactions occur, such as pruritus, respiratory depression, or nausea, they can usually be easily reversed by the administration of a specific antagonist, naloxone. An obvious drawback to intrathecal morphine is the need to perform a lumbar puncture with the resulting possibility of the development of post-dural-puncture headache, especially in obstetrical patients. However, the use of a 26-gauge spinal needle appears to decrease this problem effectively.

The use of intrathecal morphine in this parturient with CF provided selective maternal analgesia, permitted safe delivery of the neonate, and obviated the physiologic trespass that other anesthetic techniques might have incurred.

References

1. Shwachman HL. Harrison's principles of internal medicine. In: Isselbacher KJ, Adams RO, Braunwald E, eds. New York: McGraw Hill Book Co., 1980:1233-4.
2. Larsen JW. Cystic fibrosis and pregnancy. *Obstet Gynecol* 1972;39:880-3.
3. Navy MJ, Tyler JM, Shwachman H, et al. Cystic fibrosis and pregnancy. Report of a case, with a study of pulmonary function and arterial blood gases. *Obstet Gynecol* 1967;30:530-6.
4. Hughes SC, Rosen MA, Shnider SM, Abboud TK, Stefani SJ, Norton M. Maternal and neonatal effects of epidural morphine for labor and delivery. *Anesth Analg* 1984;63:319-24.
5. Baraka A, Noveihid R, Hajj S. Intrathecal injection of morphine for obstetric analgesia. *Anesthesiology* 1981;54:136-40.
6. Yaksh TL, Wilson PR, Kaiko RF. Analgesia produced by a spinal action of morphine and effects upon parturition in the rat. *Anesthesiology* 1979;51:386-92.

A Foam Cuff Endotracheal Tube T-Piece System for Use with Nitrous Oxide Anesthesia

Scott J. Greene, MD, Roy D. Cane, MBBCh, FFA(SA), and Barry A. Shapiro, MD

The purpose of the cuff on an endotracheal tube (ET) is to seal the airway, thereby permitting positive pressure ventilation (PPV) and protecting the airway from aspiration of foreign materials in the mouth and pharynx. Excessive intracuff pressure may produce tracheal ischemia, a critical factor in the genesis of major tracheal complications (1). Cross (2) has shown that the pressure in the arteriolar end of capillaries in tracheal mucosa is approximately 30 mm Hg. To prevent tracheal ischemia, intracuff pressure should be maintained at less than the arterial end-capillary pressure (3).

Nitrous oxide (N_2O) anesthesia with PPV delivered by means of a cuffed endotracheal tube is associated with increased intracuff volume and pressure because of diffusion of nitrous oxide into closed gas spaces (4). Connecting the air-filled cuff of an ET to the airway via a T-piece would allow any N_2O that diffused into the cuff to return to the airway and thus prevent excessive increases in intracuff volume and pressure. During inspiration intracuff pressure would approximate pressure in the airway thereby maintaining a seal. However, during expiration the airway would be inadequately sealed to prevent aspiration.

Because a foam-filled cuff ET open to atmosphere provides an adequate seal during expiration (5), equalizing the cuff pressure to airway pressure throughout the ventilatory cycle with a foam-filled cuff ET should obviate the increase in intracuff pressure caused by exposure to nitrous oxide and provide an adequate seal during peak inspiratory pressure with PPV. This study compares intracuff pressures in two cuff systems ventilated with and without N_2O .

Methods

This ex vivo study was conducted with an Imatrach adult tracheal model with two 1-L anesthesia bags

attached to the bronchi. The tracheal model was intubated with a PVC endotracheal tube with a high volume, low pressure air-filled cuff (AFC) (National Catheter Corp. Model #86111, 86113, 86115) inflated with the minimal leak technique at a constant airway pressure of 25 cm H_2O . The model was then ventilated with a Dräger ventilator at 10 breaths per minute, with tidal volume adjusted to maintain a peak airway pressure of 20 cm H_2O . Cuff pressure was monitored using a Bentley pressure transducer with a Narko pressure amplifier. Peak inspiratory and end-expiratory airway and intracuff pressures were recorded at 5-min intervals for 30 min during ventilation with oxygen and N_2O in ratios of 100:0, 50:50 and 30:70. The model was then intubated with a Bivona PVC endotracheal tube with a foam-filled cuff (FFC) (Bivona Fome Cuf Endotracheal Tube) connected to a T-piece inserted between the ventilator circuit and the endotracheal tube, and the measurements repeated. Measurements were made with 7, 8, and 9, size ET.

The observed intracuff pressures were plotted against time, and comparisons made between the slopes of the regression lines for the two types of cuffs. With each gas mixture comparisons of the mean cuff pressures at time zero and 30 min were made with Student's *t*-Test. *P* values of < 0.01 were considered statistically significant.

Results

Endotracheal tube size had no significant effect on cuff pressures, therefore data were pooled for analysis. The values reported are the means \pm standard deviations of all measurements made in the three different-sized ET tubes at each time point. As seen in Table 1, peak inspiratory and end-expiratory AFC cuff pressures increased with time when ventilated with 50% and 70% N_2O . After 30 min ventilation of the model with 50% N_2O , mean peak inspiratory intracuff pressure increased from 22.7 ± 0.6 mm Hg to 54.0 ± 1.0 mm Hg. Similarly, 30 min of ventilation with 70% N_2O resulted in mean peak inspiratory in-

Received from the Department of Anesthesia, Northwestern University Medical School, Chicago, Illinois. Accepted for publication July 18, 1986.

Address correspondence to Roy D. Cane, Associate Medical Director, Division of Respiratory/Critical Care, Department of Anesthesia, 250 East Superior, #678, Chicago, IL 60611.

Table 1. Mean Peak Inspiratory and End-Expiratory^a Intracuff Pressures

Time (min)	100% O ₂		50% N ₂ O, 50% O ₂		70% N ₂ O, 30% O ₂	
	Air cuff	Foam cuff	Air cuff	Foam cuff	Air cuff	Foam cuff
0	22.3 ± 0.6 (18.3 ± 1.2)	19.7 ± 0.6 (2.0 ± 0)	22.7 ± 0.6 (18.3 ± 1.2)	20.0 ± 0 (2.0 ± 0)	22.3 ± 0.6 (18.3 ± 0.6)	19.7 ± 0.6 (2.3 ± 0.6)
5	22.7 ± 0.6 (18.3 ± 1.2)	19.7 ± 0.6 (2.0 ± 0)	26.0 ± 1.0 (22.7 ± 1.5)	19.3 ± 0.6 (1.7 ± 0.6)	29.0 ± 1.7 (25.0 ± 1.7)	20.0 ± 0 (2.0 ± 1.0)
10	22.3 ± 1.2 (18.7 ± 1.5)	19.6 ± 0.5 (2.0 ± 0)	33.7 ± 2.3 (29.7 ± 1.5)	19.7 ± 0.5 (2.0 ± 0)	36.7 ± 1.2 (33.3 ± 1.5)	20.0 ± 0 (2.0 ± 0)
15	22.7 ± 0.6 (18.7 ± 0.6)	19.7 ± 0.6 (2.0 ± 0)	37.6 ± 1.5 (35.0 ± 1.0)	19.7 ± 0.6 (2.3 ± 0.6)	45.0 ± 4.0 (42.3 ± 3.5)	19.3 ± 0.6 (2.3 ± 0.6)
20	22.7 ± 0.6 (18.0 ± 1.0)	19.7 ± 0.6 (2.0 ± 0)	44.3 ± 0.6 (41.3 ± 0.6)	20.0 ± 0 (2.0 ± 0)	53.7 ± 4.5 (51.0 ± 4.0)	20.0 ± 0 (2.0 ± 0)
25	22.3 ± 1.2 (18.7 ± 1.5)	20.0 ± 0 (2.0 ± 0)	49.7 ± 0.6 (47.0 ± 1.0)	19.7 ± 0.6 (2.0 ± 0)	59.3 ± 3.5 (57.3 ± 3.5)	19.7 ± 0.6 (2.0 ± 0)
30	22.7 ± 0.6 (18.3 ± 1.2)	20.0 ± 0 (2.0 ± 0)	54.0 ± 1.0 (52.0 ± 1.0)	20.0 ± 0 (2.0 ± 0)	67.6 ± 4.0 (65.6 ± 4.0)	20.0 ± 0 (2.0 ± 0)

Values are mean ± SD expressed in mm Hg.

^aEnd-expiratory pressures are in parentheses.

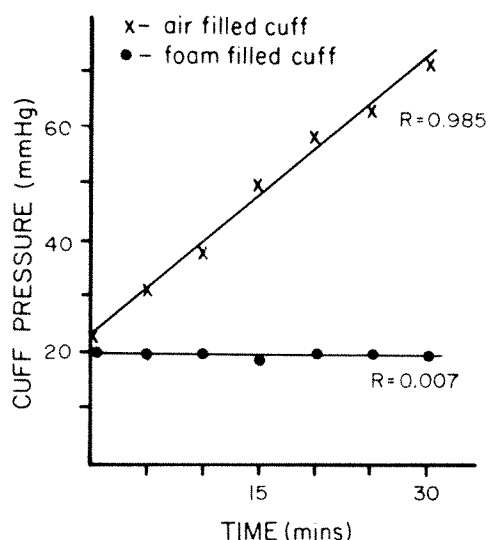


Figure 1. Relationship of cuff pressure and time for AFC (x) and FFC (•) cuffs during ventilation with 70% N₂O.

tracuff pressures increasing from 22.3 ± 0.6 to 67.6 ± 4.0 mm Hg. Mean end-expiratory intracuff pressure increased from 18.3 ± 1.2 to 52.0 ± 1.0 mm Hg with 30 min of ventilation with 50% N₂O and from 18.3 ± 0.6 to 65.6 ± 4.0 mm Hg with 30 min ventilation with 70% N₂O. These differences in mean cuff pressures at time zero and 30 min were statistically significant ($P < 0.005$). Cuff pressures did not change with time in the AFC when ventilated with 100% oxygen or in the FFC when ventilated with any of the gas mixtures. Air-filled cuff pressures were greater than FFC pressures under all conditions studied.

Regression lines for cuff pressures against time were then plotted. Figure 1 shows regression lines obtained with 70% N₂O that are similar to those found with

50% N₂O. The R value for the AFC ventilated with 50% or 70% N₂O was never less than 0.985 and was 0.012 with 100% oxygen. The R value for the FFC was never more than 0.007 with any gas mixture studied. The slopes of the regression lines are significantly different ($P < 0.001$).

Discussion

These data confirm previous findings that within 15 min of the use of N₂O, safe intracuff pressures are exceeded when using the AFC. The FFC connected to the airway effectively obviates the problem of increasing cuff pressure in the presence of N₂O.

Comparing list prices for Chicago, Illinois of PVC air-filled cuffed endotracheal tube (\$5.72, \$3.78) with that of the PVC foam-filled cuffed endotracheal tube (\$2.95) reveals that the new PVC foam cuff endotracheal tube with a T-piece offers a cost effective means of assuring that intracuff pressure will approximate airway pressure throughout the ventilatory cycle. This reduces the risks of high cuff-to-tracheal wall pressures during N₂O anesthesia, while ensuring a tracheal seal throughout the ventilatory cycle.

References

1. Trout C. Artificial airways: tubes and trachs. *Resp Care* 1976;21:513-20.
2. Cross DE. Recent developments in tracheal cuffs. *Resuscitation* 1973;2:22-81.
3. Blanc V, Tremblay NAG. The complications of tracheal intubation: a new classification with a review of the literature. *Anesth Analg* 1974;53:202-13.
4. Stanley TH. Nitrous oxide and pressures and volumes of high and low pressure endotracheal-tube cuffs in intubated patients. *Anesthesiology* 1975;42:637-40.
5. Kamen JM, Wilkinson CJ. A new low-pressure cuff for endotracheal tube. *Anesthesiology* 1971;34:482-5.

Glass Particle Contamination in Single-Dose Ampules

Karen B. Carbone-Traber MD, and Colin A. Shanks, MD

Single-dose glass ampules have been developed for ease of administration, accuracy of measurement of dosage, sterility, and use in prepackaged procedure kits. Glass particle fragmentation and ampule contamination upon opening has been previously described in the literature (1-9). In a recent editorial, Waller and George discuss particulate contamination in intravenous solutions and in glass ampules after they have been opened (9). They note the reduction of phlebitis with in-line filtration of intravenous solutions. They suggest, as do others, that filtration will reduce the risk of contamination and is a "sensible precaution" after opening of glass ampules. To date, however, a randomized, blinded, controlled study of the efficacy of filtration of glass ampules is lacking. The purpose of this study was twofold. The first phase was designed to examine glass particle contamination as a function of ampule size and the second phase to be a randomized, blinded, controlled study of glass particle contamination after aspiration of the contents of the ampule using needles of different sizes with and without a filter attached to the needle.

Methods

Phase I

Three sizes (1, 5, and 20 ml) of single-dose glass ampules were examined. For each size, ten ampules from the same manufacturer lot number were opened by hand without use of special devices. From each ampule, the entire contents were withdrawn into a 3 mm internal diameter tubing attached to a prewashed 10-ml plastic syringe. The ampules were then rinsed in triplicate with sterile water with one-third the ampule's volume each time. Both the original contents and the rinsing solutions were then filtered through a Durapore Filter 0.22 micron 47 mm in a Buchner

funnel on a vacuum flask apparatus. While the filters were still wet, they were examined under a light microscope with a 10 \times power lens. Using a complete grid search pattern, the total number of glass particles on the filter paper was recorded.

Phase II

The effect of using different needle gauges or a filter needle on glass particle contamination was examined. Forty 5-ml glass ampules from the same manufacturer lot number were randomly assigned to one of four groups based on the technique used for ampule aspiration: group 1, 3 mm plastic tubing (control); group 2, 18-gauge 3.8 cm needle; group 3, 25-gauge 1.6 cm needle; and group 4, 5-micron 19-gauge 2.5 cm Milipore filter needle. The ampules were opened in the same fashion as in phase I and the contents aspirated (without rinsing) into a 10-ml prewashed syringe using the needle or tubing according to their random number table assignment. The aspirating device was removed and the numbered, capped syringes were then taken into another room where a second person, blinded to the randomization, filtered the syringe contents and counted glass particles under a low power light microscope as in phase I.

Group comparisons of the number of particles found were made by ANOVA, followed by an Neuman-Kuel test. A $P < 0.05$ was considered statistically significant.

Results

Phase I

An example of glass particle contamination on the filter paper under low power light microscope is shown in Figure 1. Glass particles are readily identified as a result of their birefringence. Phase I data are summarized in Table 1. The mean number of glass particles from 1-ml ampules was 14 ± 4 , from 5-ml ampules was 28 ± 6 and from 20-ml ampules was 32 ± 6 . Particle size ranged between 10 and 1000 microns. Glass particle contamination in 1-ml ampules was significantly less than with 5- or 20-ml ampules. There

Received from the Department of Anesthesiology, Northwestern University Medical School, Chicago, IL. Accepted for publication July 18, 1986.

Address correspondence to Dr. Shanks, Department of Anesthesiology, Northwestern University Medical School, 303 East Chicago Ave, Chicago, IL 60611.



Figure 1. Illustration of a 400- μ m (w) \times 900- μ m (h) glass particle viewed under a low power field. Glass particles ranged in size from 10 μ m to 1000 μ m.

was no significant difference between the 5- and the 20-ml ampule glass particle contamination.

Phase II

Data are summarized in Table 2. The mean number of glass particles filtered when aspirated through a 3-mm internal diameter bore tubing was 12 ± 5 , through an 18-gauge needle 12 ± 6 , through a 25-gauge needle 14 ± 6 and through a 5-micron filter needle 13 ± 7 . No differences in sizes were noted. There was no significant difference in the number of particles aspirated by any given technique.

Discussion

Many methods have been proposed for the determination of the extent of glass particle contamination in ampules after they have been opened. Energot et al. found that filtered microscopic examination of the entire ampule contents to be superior to visual inspection or examination of random aliquots (1). In phase I of this study, the entire contents of the ampules were aspirated and then rinsed with sterile water prior to filtering and microscopic examination. In phase II the ampule contents were aspirated, filtered, and microscopically examined without rinsing (analogous

Table 1. Results of Phase I: Ampule Size

	1 ml	5 ml	20 ml
Number of ampules	10	10	10
Number of glass particles			
Mean \pm SD	14 ± 4^a	28 ± 6	32 ± 6
Range	7-23	18-38	25-45

^aSignificantly less than 5 ml or 20 ml ampules ($P < 0.05$).

Table 2. Results of Phase II: Aspiration Technique

	3 mm tubing	18-gauge	25-gauge	Filter needle
Number of ampules	10	10	10	10
Number of glass particles				
Mean \pm SD	12 ± 5	13 ± 6	14 ± 6	13 ± 7
Range	7-23	5-24	5-20	8-29

to clinical practice). The lack of rinsing and the removal of the aspirating device prior to filtering in phase II can account for the difference in numbers of particles found in 5-ml ampules in phase I and II.

In phase I, the number of glass particle contamination was evaluated as a function of ampule size. One-milliliter ampules had significantly fewer particles than either the 5- or 20-ml ampules. The particle size did not vary with ampule size. Glass particle contamination may depend, in part, on the diameter of the opening after the top has been removed. One-milliliter ampules have a 5-mm opening in contrast with 5-ml or 20-ml ampules, which have larger apertures, (7 mm and 9 mm, respectively).

Phase II studied whether glass particle contamination could be reduced with the use of small bore needles or filter needles, as suggested by several authors (3,4,10). In a randomized, blinded fashion, fine bore needles (25 gauge) were compared with larger bore needles (18 gauge) and 3 mm tubing (control). In addition, the efficacy of a filter needle was examined. No significant differences were noted between the number glass particles between the four groups. The glass particles were able to penetrate through the filter during the force of aspiration. Thus, neither the use of small gauge needles nor filter needles protects against glass particle contamination with single-dose ampules.

Pharmaceutical companies obtain the glass ampules from two manufacturers. In order to control for the possibility of differing glass particle contamination between ampule manufacturers, ampules from a single manufacturer and, in phase II, a single lot number

were examined. The present data are restricted to one pharmaceutical company and, thus, one glass ampule manufacturer. However, the reports from Europe and Australia suggest that these data would apply regardless of the manufacturer (5,9,10,11).

To date, little is known regarding the clinical significance of intravenous, epidural, and subarachnoid injection of glass particles. There have been reports of pulmonary microemboli, thrombi, and granulomas as a result of small particle contamination of glass microflakes, rubber, cellulose fibers, plastics, antibiotic crystals, and microorganisms found in large volume intravenous infusions (12). The incidence of infusion phlebitis with intravenous solutions has been shown to decrease with the use of in-line filter devices (2). These studies were done with a low pressure infusion system. In this study, however, the addition of a filter device did not prevent glass particle contamination when the drug was tested in a "intravenous push" (high pressure) method, as we commonly use in anesthesia. Further investigation is needed in order to prevent glass ampule fragmentation and in improving the efficacy of filtering the glass particles during bolus administration.

References

1. Ernerot L, Dahlander LE. The contamination of ampoules in connection with opening. *Acta Pharm Succical* 1969;6:401-6.
2. Falchuk KH, Peterson L, McNeil BJ. Microparticulate-induced phlebitis: its prevention by in-line filtration. *N Engl J Med* 1985;312:78-82.
3. Furgang FA. Glass particles in ampules. *Anesthesiology* 1974;41:525.
4. Katz H, Borden H, Hirsher D. Glass particle contamination of color break ampules. *Anesthesiology* 1973;39:354.
5. Purdue H, Punchihewa VG. Glass fragments in thiopentone sodium solution. *Anaesthesia* 1982;37:101-2.
6. Stebbins WE, Florey HW. The behavior of intravenously injected particles observed in chambers in rabbits' ears. *Q J Exp Physiol* 1960;45:252-64.
7. Turco S, Davis NM. Preventing the injection of glass particles with furosemide solution. *Hospital Pharmacy* 1972;7:423-4.
8. Turco S, Davis DM. Glass particle in intravenous injections. *N Engl J Med* 1972;287:1204-5.
9. Waller DG, George CF. Ampoules, infusions, and filters. *Br Med J* 1986;292:714-5.
10. Shaw NJ, Lyall EGH. Hazards of glass ampules. *Br Med J* 1985;291:1390.
11. Gillies IR, Thiel WJ, Oppenheim RC. Particulate contamination of Australian ampoules. *J Pharm Pharmacol* 1986;38:87-92.
12. Garvan JM, Gunner BW. The harmful effects of particles in intravenous fluids. *Med J Aust* 1964;ii:1-6.

Letters to the Editor

A Visual Warning Device for Improved Safety

To the Editor:

In the ongoing attempt to improve patient safety, anesthesia providers must constantly search for the means to eliminate any anesthesia mishap. Many authors have demonstrated that lapses of vigilance are frequently the cause of anesthesia mishaps (1-3). Unfortunately, it has also been demonstrated that vigilance decreases with the duration of anesthesia, which may be accentuated by the increased demands of mental and/or physical activity. It is also recognized that the design of anesthesia equipment has a strong influence on the mishap rate (1,4,5).

We would like to address a problem that has led to several preventable anesthesia mishaps. This problem could be largely eliminated with changes in equipment design.

The problem was highlighted in the ASA patient safety film "Human Error in Anesthesia" (6) and resulted from an anesthetic vaporizer being inadvertently left in the "ON" position when it was not the intent to use that inhalation agent. In discussing this particular occurrence, several experienced practitioners were able to recall similar incidents in their own practice or that of a colleague. One practitioner recalled a situation where a patient had been unintentionally given oxygen and enflurane through a nasal cannula that was connected to the anesthetic machine's common gas outlet. This was the result of a vaporizer being left on from a previous case.

We believe the incidence of patients unintentionally receiving anesthetic agents could be reduced if modifications were made to new machines and retrofitted to existing machines. The modifications involve a device that would trigger a switch (activated by turning on a vaporizer) that would light a color-coded panel light. Many currently used vaporizers have a cam-projection on the concentration setting dial that could be retrofitted with a cam-activated light switch. Other types of switches could be devised and fitted to vaporizers that do not have cam-projections. The light panel could be mounted in a conspicuous place on the anesthesia machine, preferably near the rotameter display module.

Whenever a vaporizer is turned on, the color-coded light would indicate that a vaporizer is "ON" and would indicate which agent is being delivered. As with any warning device, this light could inadvertently be ignored, but the likelihood would be considerably reduced. Additionally, any personnel in the operating room or a consultant called into the room during a problem situation would immediately have a greater opportunity to notice that a vaporizer is on and delivering an anesthetic agent.

The technical problems of how to develop this system and fit it to older machines should provide a challenge to anesthesia equipment designers.

While no equipment change can ever be substituted for vigilance, improvements in design that reduce chances of human error should always be pursued. We believe the design change we have described could significantly improve patient safety in anesthesia. We would hope that equipment manufacturers will actively look for ways to incorporate the suggested design change.

Lynn Williams, MB, BS, FFARCS

Charles Barton, CRNA

John R. McVey, MD
*Anesthesiology Department
Aultman Hospital*

Jan D. Smith, MB, MRCP

*Department of Anesthesia
Northeastern Ohio Universities College of Medicine
Canton, OH 44708*

References

1. Cooper JB, et al. Preventable anesthetic mishaps: a study of human factors. *Anesthesiology* 1978;49:399-406.
 2. Utting JE, Gray TC, Shelley FC. Human misadventures in anaesthesia. *Can Anaesth Soc J* 1979;26:472-8.
 3. Lunn JN, Mushin WW. Mortality associated with anaesthesia. London: Nuffield Provincial Hospital Trust, 1982.
 4. Cooper JB, Newbower RS, Kitz RJ. Anesthesia management: considerations for prevention and detection. *Anesthesiology* 1984;60:34-42.
 5. Dorsch JA, Dorsch SE. Hazards of anesthesia machine and breathing systems, PP 289-325. In: *Understanding anesthesia equipment: construction, care and complications*. Baltimore: Williams and Wilkins, 1984.
 6. Human error in anesthesia: patient safety program (videotape). American Society of Anesthesiologists, 1985.
-

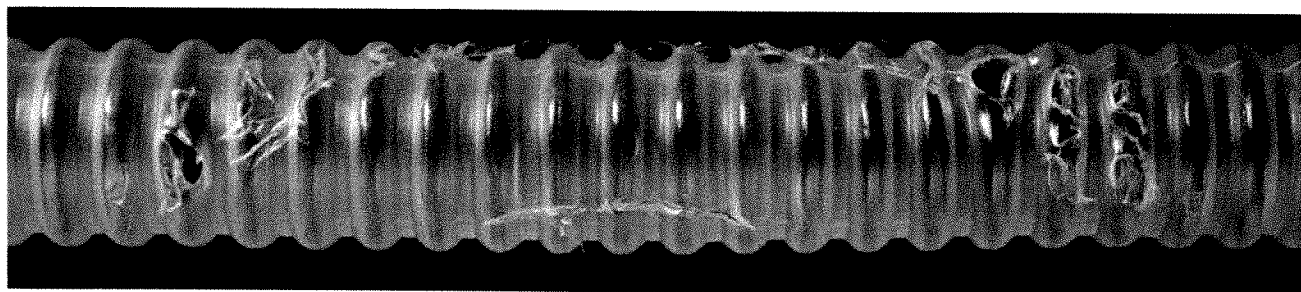


Figure 1. Several small holes in corrugated tubing are visible when traction is applied to stretch the tubing. Adherent shreds of plastic packaging material are also visible.

Unusual Corrugated Tubing Leak

To The Editor:

Despite use of a scavenging device, the odor of a potent inhalation agent being used became apparent during the administration of general endotracheal anesthesia to a child. A check of the scavenging system showed it to be functioning properly. Visual inspection of the anesthetic circuit revealed several small holes in the disposable corrugated plastic tubing of the inspiratory limb of the circle system (Fig. 1). A brief (5-sec) check of the integrity of the "low-pressure" circuit before beginning anesthesia had not revealed the presence of a leak. The circuit was changed, and the anesthetic concluded uneventfully.

To test the integrity of a circle system, Dorsch and Dorsch (1) recommend occluding the Y-piece of the circle system and flushing the system with oxygen to achieve a pressure of 300–400 mm H₂O. With no additional gas flow, pressure should not decrease more than 50 mm H₂O in 30 sec. Alternatively, the breathing system can be pressurized to 300 mm H₂O and the oxygen flow set to 100 ml/min. If the pressure continues to increase (i.e., the inflow exceeds outflow), the leakage is considered to be within acceptable limits.

Subsequent testing with the faulty inspiratory limb showed the leakage to exceed the criteria of Dorsch and Dorsch when the tubing was stretched, but not when it was not stretched and under tension. Thus, even routinely accepted testing would not have disclosed the leakage in this circuit before beginning the anesthetic. The odor of the potent inhalational agent became apparent only after the position of the operating table was altered in such a way as to stretch the corrugated tubing and thus permit the leak to occur.

This occurrence underscores the need for constant vigilance during the conduct of an anesthetic. Any unusual occurrence—including detection of the odor of an anesthetic agent at an unexpected time—should prompt a meticulous search for possible mechanical problems with either the breathing circuit or the anesthesia machine.

In this case, it appeared that a heated sealing device used to close the plastic packaging material about the circuit in-

advertently applied heat to the breathing circuit and to the plastic packaging material at the same time.

Thomas J. Poulton, MD
Department of Anesthesiology
Creighton University School of Medicine
Omaha, NE 68131

Reference

1. Dorsch JA, Dorsch SE. Understanding anesthesia equipment. 2nd ed. p.405. Baltimore: Williams and Wilkins, 1984.

Induction of Anesthesia with Isoflurane in Children

To the Editor:

The study reported by Kingston (Anesth Analg 1986;65:181–4) cannot be regarded as a comparative study of the time required to induce anesthesia with isoflurane and halothane in children; equal increments in the inspired concentration of the two agents were not administered at equal times by the author's own admission; and, because topical anesthesia was used, the times to tracheal intubation are not relevant. The study is therefore a commentary on the author's experience with isoflurane in 20 children, an experience that shows a remarkable difference from our findings (Anesthesia 1985;40:315–23).

Our study was performed in the first 248 unselected children who presented for anesthesia when isoflurane became available to us in 1983. The children ranged in age from 3 months to 14 yr, and included nine children presenting for surgery for the relief of severe tracheal obstruction and 13 children for nasal surgery, whose nostrils were obstructed with cocaine/epinephrine packs. In these difficult conditions, 22 patients (8%) coughed during induction, an incidence considerably less than the 20% quoted by Kingston. The time to loss of consciousness (indicated by the disappearance of the eyelash reflex) was 84 ± 24 sec in 99 children who were described as alert despite preoperative medication, and 90 ± 30 sec in 16 children who had received no preoperative medication. Both of these times

are less than a quarter of the time to loss of conjugate gaze with either halothane or isoflurane quoted by Kingston; our time to tracheal intubation with isoflurane (without neuromuscular blockade or topical anesthesia, and with spontaneous ventilation throughout the procedure) in 49 children was 252 ± 30 sec, which is also considerably less than the times to loss of conjugate gaze with either agent quoted by Kingston.

In view of the central role played by inhalation anesthesia in such critical situations as failed intubation, the factors that lie behind the difference between our study and Kingston's, and the study by Pandit et al. that Kingston cited (Anesthesiology 1982;59:A445), demand further scrutiny.

W.S. Wren, FFARCSI, FFARCS
Department of Anesthetics,
Our Lady's Hospital for Sick Children,
Dublin 12, Ireland

A.J. McShane, MRCPI, FFARCSI
Department of Anesthesiology,
Johns Hopkins Hospital,
Baltimore, MD 21213 USA

In Response:

I thank Drs. Wren and McShane for their interest in our paper and for their comments about the differences that exist between their study and ours. After reading their paper, the differences they mention are not surprising.

1. In their paper they state that all but 16 of the 248 patients were premedicated. In their letter they compare 99 premedicated patients who were "alert" with the 16 unpremedicated patients. Because a variety of premedicants were used (papaveretum and atropine, or tripropazine and meperidine or rectal thiopental), it is not unexpected that induction of anesthesia in their patients was more rapid.
2. We chose conjugate gaze as an end-point to our induction sequence, whereas they chose loss of an eyelash reflex, which occurs earlier.
3. Perhaps the biggest difference of all between these two studies lies in the ages of the patients studied and the technique used for induction of anesthesia. Our patients were children between the ages of 1 and 6 yr, whereas the children in their study ranged between 3 months and 14 yr (although in their paper they mention a patient who was 12 hr old).
4. During inhalation induction, we limited the increase in halogenated agent to an increment of 0.5% each 6 breaths, the tolerance of the child, therefore, dictating the rate at which the agent was administered. In addition, in case it was possible to achieve a higher inspired concentration more rapidly with one or another agent, we limited the maximum inhaled concentration of both agents to 1.5 MAC. Wren et al. used a T-piece or Bain system in which oxygen-nitrous oxide, 3-6 L/min, was used with an initial concentration of 1% isoflurane. This was held to the patient's faces. No attempt was made to measure what the children received, but in their discussion the authors note that "atraumatic tracheal intubation without inter-

ruption of spontaneous ventilation can be accomplished after an exposure of 2 minutes to 4% isoflurane, but the same maneuver requires an exposure of 4 minutes of 4% halothane." This would also explain why induction of anesthesia and the achievement of a plane of anesthesia sufficient to allow tracheal intubation occurred earlier in their patients. They spoke only of pulse rates, but it would have been interesting to see the changes in blood pressure that occurred when using this technique.

We found that in unpremedicated patients, even at relatively low rates of administration of isoflurane, there was an increased incidence of airway irritability; this agent appeared to offer no advantage over halothane when used in this way.

Harry G.G. Kingston, MD
Department of Anesthesiology
Oregon Health Sciences University
Portland, OR 97201

A New Device to Smooth Pediatric Inhalation Induction

To the Editor:

The goals of a smooth, pleasant, and safe induction of anesthesia may be difficult to accomplish in the pediatric patient. Although inhalation induction has become a standard technique for the child below 6 years of age, the fear of suffocation by the mask and the unpleasant smell of the agent often preclude cooperation. This results in forced mask induction of a struggling child. The use of a flavor such as peppermint or cherry inside the mask or a "steal" induction technique may provide cooperation.

We have modified our equipment for inhalation induction for the child from 2 to 6 years of age to include a toy blower. The mouthpiece of a "medication" nebulizer (Traveler 2C7161) is taped to the 18-mm end of a flexible adapter that is attached to a 1-L anesthesia bag (Fig. 1). Prior to surgery, the child can practice "blowing up the balloon" in his room in the company of his parents, without apprehension. Once in the operating room, after the application of standard monitoring equipment, the mouthpiece is attached to a semiclosed circle with the bag on the machine (Fig. 2). The child watches the bag and is encouraged to blow up the balloon just as practiced before. High flows of nitrous oxide and oxygen (7L/3L) are started through the mouthpiece, and a potent agent is gradually introduced. As the child calms down we easily switch to an appropriate mask to complete the induction.

Induction is smooth, pleasant, and the patient is cooperative. The advantage of this system seems to involve the substitution of a nonthreatening, familiar experience (blowing through a plastic mouthpiece) for the strange and frightening sensation of being suffocated by an odoriferous black mask.

We have used the technique in over fifty patients be-



Figure 1. Toy Blower: Mouthpiece of a medication nebulizer (Travenol 2C 7161) taped to a flexible adapter attached to a 1-L anesthesia bag.

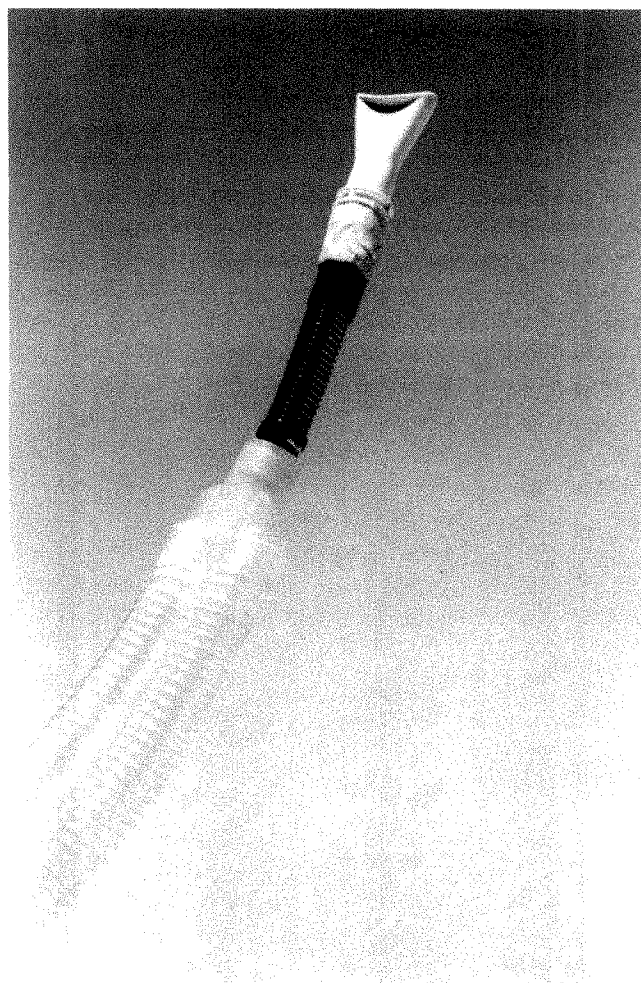


Figure 2. Mouthpiece attached to standard tubing as part of a semiclosed circle.

tween the ages of 2 and 6 years and find it provides a safe induction that minimizes anxiety and accentuates patient cooperation.

Art Smerling, MD
Ellise Delphin, MD
Department of Anesthesiology
Columbia-Presbyterian Medical Center
New York, NY 10032

On the Use of Priming with Vecuronium for Rapid Sequence Induction

To the Editor:

In the recent report on vecuronium (VEC) priming for rapid sequence induction, Kunjappan et al. (1) found that a 15-

$\mu\text{g/kg}$ VEC dose given 5 min before 85 $\mu\text{g/kg}$ VEC gave excellent intubating conditions in 81.5 sec. In advocating the 15- $\mu\text{g/kg}$ VEC priming dose, the authors state that train-of-four (TOF) response as noted by visual observation was not affected and that the heavy eyelids and blurred vision were "greatly ameliorated" by premedication.

Engbaek et al. (2) in studying unmedicated volunteers found that 15 $\mu\text{g/kg}$ VEC caused a significant decrease in quantitatively measured TOF, as well as considerable subjective symptoms and objective signs due to muscle paralysis. Even a dose of 5 $\mu\text{g/kg}$ was found to cause an unsatisfactory degree of paralysis in one patient. A recent report (3) of pulmonary aspiration after a priming dose of VEC underscores the danger involved in this technique.

In view of the untoward effects of large priming doses and the lack of efficacy of priming when a reduced priming dose is used (1,4), we suggest the abandonment of priming with VEC. Alternatively, 0.25-mg/kg of VEC given as a bolus can be employed in those patients in whom succinylcholine

is contraindicated. Lennon et al. (5) have shown that this dose will provide good intubating conditions within 1 min.

Mitchel Sosis, MD, PhD
Department of Anesthesiology
Jefferson Medical College
Philadelphia, PA 19107

References

1. Kunjappan VE, Brown EM, Alexander GD. Rapid sequence induction using vecuronium. *Anesth Analg* 1986;65:503-6.
2. Engbaek J, Howardy-Hansen P, Ording H, Viby-Mogensen J. Precurialization with vecuronium and pancuronium in awake, healthy volunteers: the influence on neuromuscular transmission and pulmonary function. *Acta Anaesthesiol Scand* 1985;29:117-20.
3. Musich J, Walts LF. Pulmonary aspiration after a priming dose of vecuronium. *Anesthesiology* 1986;64:517-9.
4. Sosis M, Stiner AE, Marr AT. Does the priming principle work? *Anesthesiology* 1985;63:A340.
5. Lennon RL, Olson RA, Gronert GA. Atracurium or vecuronium for rapid sequence endotracheal intubation. *Anesthesiology* 1986;64:510-3.

Comments on the Review of Manual of Pediatric Anesthesia

To the Editor:

A review of *A Manual of Pediatric Anesthesia*, which I edited, was published in a recent issue of *Anesthesia and Analgesia*. This review was prepared by Dr. Borland of the Department of Anesthesiology of Children's Hospital, Pittsburgh. The review unfortunately contained numerous errors of fact concerning the content of the book. The reviewer cited as omissions many topics that are covered in the appropriate sections of the book. In addition, he repeatedly misread sections of the book and referred to statements that plainly were not made within the text.

Some topics said to have been omitted, but that are in the appropriate section of the book, include the intraoperative use of somatosensory evoked potentials, the use of urine output measurements to assess fluid resuscitation in burns, the use of calcium gluconate to correct citrate toxicity, and the treatment of hyperkalemia in renal failure.

Dr. Borland has not read the book carefully. He suggests for example, "they recommend the use of a nasotracheal tube for the treatment of laryngo-tracheal bronchitis." The book does not say this. It does discuss both the use of nasotracheal intubation and tracheotomy in the treatment of laryngo-tracheal bronchitis and outlines when nasotracheal intubation might be suitable and also the cases in which tracheotomy may be required. At no place do we recommend either approach as being the preferred method.

Dr. Borland has misread the section of the treatment of laryngeal papillomatosis and has suggested that our concerns about jet ventilation relate to the possibility of the distal spread of papillomata by this mechanism. This is not what is published! The book in this section clearly outlines our concerns with jet ventilation—that if it is used distal to a laryngeal obstruction, as in patients with papillomata, it may lead to pneumomediastinum and pneumothorax.

These are just a sample of the errors of fact contained in this book review. Others are too numerous to document fully in a Letter to the Editor. These errors have, however, been fully documented in a letter to Dr. Borland.

A reviewer is certainly entitled to express his opinions about the book he or she is reviewing. However, the reviewer also has a responsibility to read the book diligently and report accurately the facts of what is contained and stated within that book. I can only suggest that those who wish to read a balanced factual review of this book should look at those reviews that have been published in other medical journals.

David J. Steward
Department of Anesthesia
Children's Hospital
Vancouver, British Columbia V6H 3V4

Preponderance of Hydrolysis in Inactivation of Atracurium: Questions Remain

To the Editor:

I read with great interest the letter by Cook et al. (1) regarding the "diametrically opposite conclusions" reached by them (2) and by us (3). We agree that the conclusions are diametrically opposite, but not for the reasons stated by Cook et al.

First, let me comment on the experiments reported by Cook et al. (2): The number of plasma donors was not specified. It appears that only a single experiment was performed. In Figure 1, the lines were drawn without experimental points. Nowhere is there a mention of estimates of variability of the data (SEM or SD). The interpretation of data shows (Figure 2) that the authors misrepresented the two degradation pathways of atracurium. First, formation of laudanosine from the "quaternary alcohol" moiety can occur *only* via Hofmann elimination and not via ester hydrolysis as they suggest. Second, formation of laudanosine from the "quaternary acid" moiety cannot occur via ester hydrolysis as they also suggest. The acid does not possess an ester group and, therefore, cannot be hydrolyzed. Their postulate that the "quaternary acid" moiety may be degraded by Hofmann elimination had not previously been suggested and for a good reason: anionic charge of the carboxylic group would have the tendency to retard Hofmann elimination. To conclude our critique, Hofmann elimination is the *only* pathway that results in formation of laudanosine. I should also add that stoichiometric considerations dictate that an equimolar amount of acrylates be generated concomitantly with laudanosine. It is, then, a matter of semantics to conclude that laudanosine alone cannot be the sole "major end-product" of atracurium, as proposed by Stiller et al. (2) and reiterated in their letter (1). Acrylate

moiety is formed simultaneously and should also be mentioned as a "major end-product."

Second, although Stiller et al. (2) cite the work of Merrett et al. (4), they did not mention the discrepancy between their data and those of Merrett et al. for the estimates of $t_{1/2}$ of atracurium in buffer and plasma. The discrepancy in the results is troublesome, because the conclusion by Stiller et al. (2) and Cook et al. (1) about the relative contributions of the two degradation pathways presumably hinges on the finding that the inactivation of atracurium proceeds "several-fold faster in plasma than in buffer" (1).

Third, the reference by Cook et al. (1) to our study is incomplete. We have shown previously (5) the effectiveness of TOTP in inhibiting the enzyme-catalyzed hydrolysis of atracurium in rats in vivo. Our follow-up in vitro study (3) demonstrated a rapid inactivation of atracurium in rat plasma and a slower inactivation rate in native human plasma. The results with the esterase inhibitor TOTP were consistent with greater enzyme-catalyzed hydrolysis of atracurium in rat than in human plasma. In support of our findings we offered, inter alia, the case report of Baraka et al. (6), that in a patient poisoned with parathion, atracurium produced normal, i.e., expected, characteristics of relaxation. The statement in the report by Stiller et al. (2) that "in patients poisoned with potent esterase inhibitors, the duration of atracurium (?) might be prolonged" represents a logical extrapolation of their postulates. However, the report by Baraka et al. (6) does not bear out their hypothesis but is compatible with our findings. Both Stiller et al. (2) and Cook et al. (1) ignored the report by Baraka et al. (6).

Finally, we did discuss (3) whether TOTP and atracurium might or might not be the appropriate inhibitor and substrate, respectively, for the human enzyme. In their letter Cook et al. merely echoed our discussion, without considering our reasons against these alternatives.

Cook et al. cite, as unpublished results, the inability of carboxylesterase (source?) to facilitate the inactivation of atracurium. Our (also unpublished) results with the commercially available pig enzyme (from Sigma Co., #E3128) show that the enzyme does catalyze the inactivation of atracurium (pH 7.4, 37°C). The experiments were repeated four times.

To summarize: we cannot offer an explanation for the finding of Stiller et al. that each molecule of atracurium produces two molecules of laudanosine and undergoes hydrolysis. Furthermore, we find it difficult to explain the finding that DIFP inhibits the spontaneous generation of laudanosine and, by inference, retards Hofmann elimination. Some of the pathways proposed by Stiller et al. are not at all possible, some are just unlikely.

Vladimir Nigrovic, MD
Departments of Anesthesiology and Pharmacology
Medical College of Ohio
Toledo, OH 43699

References

1. Cook DR, Stiller R, Ingram M. In vitro degradation of atracurium. *Anesth Analg* 1986;65:543.
2. Stiller RL, Cook DR, Chakraborti S. In vitro degradation of atracurium in human plasma. *Br J Anaesth* 1985;57:1085-8.
3. Nigrovic V, Pandya JB, Auen M, Wajskol A. Inactivation of atracurium in human and rat plasma. *Anesth Analg* 1985;64:1047-52.
4. Merrett RA, Thompson CW, Webb FW. In vitro degradation of atracurium in human plasma. *Br J Anaesth* 1983;55:61-6.
5. Nigrovic V, Auen M, Wajskol A. Enzymatic hydrolysis of atracurium in vivo. *Anesthesiology* 1985;62:606-9.
6. Baraka A, Cara L, Jaoude CA. Atracurium v. suxamethonium in a case of organophosphorous poisoning. *Br J Anaesth* 1984;56:673.

Variability of Fentanyl Pharmacokinetics in Neonates

To the Editor:

The data on fentanyl pharmacokinetics in neonates reported by Koehtop et al. (1) exhibit considerable variability. The coefficients of variation [standard deviation/mean] $\times 100\%$ of the derived pharmacokinetic variables for most drugs do not exceed 30-40% (2). In contrast, the coefficients of variation for the distribution volumes, clearance, and elimination half-time determined by Koehtop et al. range from 73 to 91%. Even in their most homogeneous group, the infants all 1 day old of normal weight undergoing myelomeningocele repair, the coefficient of variation of the elimination half-time is 90%. I am concerned that this high degree of variability may be the result of some aspects of their study design and data analysis.

The duration of fentanyl infusion differed, and there is no indication that this was taken into account when the pharmacokinetic models were fit to the data. Estimates of pharmacokinetic variables will be incorrect if the infusion time is not taken into account (3), especially for drugs like fentanyl that have short distribution half-times. No consistent blood sampling protocol was followed, and time at which the last sample was collected varied from 5 to 20 hr after injection of fentanyl. This could have resulted in additional variability because the duration of blood sampling is a critical determinant of the estimated elimination half-time (4).

Although various criteria for comparing different models and weights are cited, no rigorous method of model specification is given (1). This is very important because "forcing" an inappropriate model on a data set will result in incorrect estimates of pharmacokinetic variables. In their figure, it is obvious that the model does not even come close to approximating the elimination phase data for patient 13. The elimination half-time is grossly underestimated. Although one cannot be certain without seeing the raw data, it appears as though a biexponential model was forced onto the data. If the triexponential model was also unable to characterize the data, this suggests that the kinetics of fentanyl were nonlinear in that patient, which would invalidate any conclusions based upon a linear model. Similarly, accurate estimation of pharmacokinetic variables is impossible if the timing and/or magnitude of secondary peaks precludes accurate fitting of a linear model to the data. This may have occurred in as many as seven of their 14 patients.

R.J. Hudson, MD, FRCP(C)
Department of Anesthesia
University of Manitoba
Winnipeg, Manitoba, Canada R2H 2AG

References

1. Koehntop DE, Rodman JH, Brundage DM, Hegland MG, Buckley JJ. Fentanyl pharmacokinetics in neonates. *Anesth Analg* 1986;65:227-32.
2. Benet LZ, Scheiner LB. Design and optimization of dosage regimens: pharmacokinetic data. In: Gilman AG, Goodman LS, Gilman A, eds. *The pharmacological basis of therapeutics*. 6th ed. New York: MacMillan, 1980:1684-1737.
3. Loo JCK, Riegelman S. Assessment of pharmacokinetic constants from post-infusion blood curves obtained after iv infusion. *J Pharm Sci* 1970;59:53-5.
4. Gibaldi M, Weintraub H. Some considerations as to the determination and significance of biologic half-life. *J Pharm Sci* 1971;60:624-6.

In Response:

We disagree with Dr. Hudson's contention that the variability of pharmacokinetic parameter estimate for fentanyl we reported (1) is greater than that commonly observed for other drugs. In fact, the variability found for fentanyl is similar to drugs studied under similar conditions; we cite lidocaine as one example (2). Fentanyl disposition in these patients was studied during major surgical procedures and acute stress. It would be surprising if pharmacokinetic variability was *not* greater than that found in non-acutely ill patients receiving chronic therapy or in normal volunteers, which provides the basis for the textbook reference cited.

Dr. Hudson raises several issues relative to design and data analysis as possible contributing factors to the variability we reported. The infusion time was recorded and appropriately accounted for when we compiled the data as is described in detail in reference 4 of the original publication. In contrast to Dr. Hudson's contention that "no consistent blood sampling protocol was followed . . .," the methods clearly state that samples were obtained 1, 5, 10, 20, 40, 60, and 120 min. Samples during this time spanned the duration of the surgical procedures. He is correct that there were subsequent samples obtained at variable times, but it does not then follow that these variable sampling times influenced the precision of parameter estimates. As is very nicely illustrated by D'Argenio (3), the use of a fixed, geometrically spaced sampling scheme does not alleviate and, in fact, is "sub-optimal" even in the presence of uniform model parameter values. Nonuniform time of samples does not necessarily result in additional variability. The variable late sampling times were in part an effort to collect samples sufficiently late in disposition to more accurately estimate elimination. On a more practical level, there are major logistical difficulties in conducting pharmacokinetic studies in patients such as those who were the subject of this report and these logistical constraints were certainly a

factor in the variable sampling times after the initial 2 hr. With a mean of 8.3 samples collected over an average interval of 6.9 hr, we feel our parameter estimates are reflective of fentanyl disposition.

The last major point raised is more problematic. Model discrimination is difficult under the best of circumstances and there is no "rigorous method" available (4). The use of an F-ratio may be of some help but is not statistically adequate for models with non-linear output and of varying order. Careful examination of the data is probably the most useful, albeit unsatisfactory, approach currently available for assessing a model's fit to data.

Dr. Hudson misconstrues our results regarding fitting a three-compartment model to the data. We were, contrary to his assertion, able to fit a three-compartment model to the data but without any improvement over a two-compartment model as determined by comparative sums of squares. In any case, this would not, without other supporting evidence, warrant entertaining non-linearity of elimination. A compartment model was not always entirely satisfactory, e.g., patient 13-Figure 1; and it is quite possible that a physiologic model with time varying parameters would be preferable but is obviously not possible from plasma concentration data alone. We do point out in our paper that in certain situations, e.g., rebound phenomena, "fentanyl plasma levels . . . were not well-described by a compartment model." The clearance and $V_{d_{ss}}$ parameters reported are noncompartmental and may provide some help in such situations. The limitations of compartment modeling were recognized and acknowledged in the discussion but do not invalidate any conclusions drawn.

John Rodman, PHARM D
Pharmaceutical Division
Pharmacokinetics and Pharmacodynamics Section
St. Jude Children's Research Hospital
Memphis, TN 38101

Douglas E. Koehntop, MD
Department of Anesthesiology
University of Minnesota
Minneapolis, MN 55455

References

1. Koehntop DE, Rodman JH, et al. Pharmacokinetics of fentanyl in neonates. *Anesth Analg* 1986;65:227-32.
2. Rodman JH. Lidocaine. In: Evans WE, Schentag JJ, Jusko WJ, eds. *Applied pharmacokinetics: principles of therapeutic drug monitoring*. 1st ed. San Francisco: Applied Therapeutics, 1980:350-92.
3. D'Argenio DZ. Optimal sampling times for pharmacokinetic experiments. *J Pharmacokin Biopharm* 1981;9:739-56.
4. Godfrey K. Some practical problems in compartmental modeling. In: *Compartmental models and their application*. New York: Academic Press, 1983:146-274.

Book Reviews

Molecular and Cellular Mechanisms of Anesthetics

Sheldon H. Roth and Keith W. Miller, eds. New York: Plenum Medical Book Co., 1986, 490 pp, \$59.50.

This is the report of the Third Conference on Molecular and Cellular Mechanisms of Anesthetics, a symposium held in Calgary, Alberta, during May 1985, in honor of B. Raymond Fink. It continues the series of publications of such conferences, which began in Paris in 1950 and continued in Seattle between 1966 and 1980. An overview of the past five years, it is the latest summary of progress for those interested in the challenges of the mechanisms of anesthesia.

There were 114 participants from the US, Canada, England, Australia, Israel, and Japan. The presentations were grouped as follows (discussions are not included): Cellular Actions of Anesthetics, eight papers; Postsynaptic Actions of Anesthetics, seven papers; Anesthetics and Sodium Channels, five; Biophysical Mechanisms of Anesthetics, six; Pressure-Anesthetic Interactions, four; Toxicity of Local Anesthetics, four; and Toxicity of General Anesthetics (all on hepatic dysfunction), four papers.

The symposium is best summed up by Dr. Fink himself in the foreword:

"This book captures the fine, invigorating ambience of the University of Calgary and the exciting explorations and companionship of a gathering in a frontier territory of neuroscience . . . [It has] progressively refined the quarry, from pathway to synapse to lipoprotein membrane to receptor and single channel, in heuristic convergences of neuronal physiology, biochemistry, and pharmacology. Nevertheless, the anesthesiologist in me senses a certain disquiet, a certain claustrophobia provoked by the narrow confines of micropipettes. How much more tubular must tunnel vision become before the desired broad view emerges? . . . The advances in molecular neurobiology seem continually to increase the apparent complexity of the total problem and the conceptual distance between the reductionists in the laboratories and the holists in the operating rooms.

"Perhaps . . . it is worth recalling yet again that the extraordinary diversity of molecules that can induce general anesthesia is matched by the diversity in detail of the anesthetic syndromes they produce, and more than matched by the diversity of proteins and lipoproteins in neuronal

membranes. Thus it may be an oversimplification to regard general anesthesia, or even the loss of consciousness, as a single 'state' of depression of the nervous system, and closer to reality to regard each as a pharmacological syndrome in a pharmacological spectrum of syndromes . . . In the old days of diethyl ether we used to divide anesthesia into a number of stages and planes distinguished on the basis of motor responses, and made guesses or experimental inferences about the related sites of central nervous depression. It was a time of unified theories, focusing on which phase—aqueous, lipid, or lipoprotein—was the seat of what one might call the biophysical field effect of anesthetics. A needle-eyed reappraisal is now proceeding, centering on receptor-ligand interactions, where the diversity alluded to previously can be easily accommodated."

Gerald A. Gronert, MD
Professor of Anesthesiology
University of California Davis
Davis, CA 95616

Invasive Procedures in Critical Care

Charles L. Sprung and Ake Grenvik eds. New York: Churchill-Livingstone, 1985, 294 pp, \$39.00.

This multi-authored text is the seventh volume in the series *Clinics in Critical Care Medicine*. The editors' goal is to review procedures performed frequently, as well as less commonly, in intensive care units. They acknowledge that these procedures are performed by and for physicians of various backgrounds and specialties working in intensive care units. The text is well-organized, with 14 chapters that systematically cover the "indications, contraindications, methods, hazards, and complications" of procedures performed on critically ill patients. The editors emphasize the crossover expertise required of intensivists to determine when to perform outlined techniques and interpret data derived from such measures. Initial chapters include the more common procedures such as vascular access techniques and methods for the establishment of an airway. Next, diagnostic techniques including paracentesis, peritoneal lavage, thoracentesis, bronchoscopy, GI endoscopy, and ICP monitoring are well-covered. Finally, therapeutic maneuvers such as dialysis, cardiac pacing, pericardiocentesis, intraaortic balloon

pumping, and chest tube placement are reviewed in individual chapters.

This book is well-conceived and covers almost all areas of invasive procedures required in the day-to-day intensive care management of adult patients. The book has been edited well and is without major errors, typos, or omissions. Special strengths of this book are the extensive and excellent bibliography in each chapter, a well-organized index, the consistent organization of each section, and superior coverage of ICP monitoring, peritoneal lavage, and dialysis. These features make this book a valuable resource for those studying for the forthcoming subspecialty certification examinations in Critical Care Medicine. Therefore I would recommend the addition of this readable text to the library of residents and physicians from all the major ICU specialties. The preliminary chapters would also be useful as teaching references for medical students.

Douglas B. Coursin, MD
Assistant Professor of Anesthesiology and Medicine
University of Wisconsin Clinical Science Center
Madison, WI 53792

Basic Physics and Measurement in Anesthesia (second edition)

G. D. Parbrook, P. D. Davis, and E. O. Parbrook.
Norwalk, CT: Appleton-Century-Crofts, 1986, 354 pp.
\$34.95.

Many of the basic principles involved in the applied physiology and pharmacology of anesthesia find their roots in physics. Modern anesthesia is becoming increasingly technology-oriented and dependent. In spite of "user friendly" aspects of many of the new devices, it is essential that the anesthesiologist understand the basic physics upon which these measurements are founded. Only in this way can we evaluate the accuracy, calibration, and limitations of the modern anesthesia machines and monitoring devices. In this context, the second edition of *Basic Physics and Measurement in Anesthesia* has been written for the clinical anesthesiologist to review and strengthen his or her understanding of applied physics. This book encompasses a wide range of practical applications of physical principles to the every day practice of anesthesia. Physical laws are stated, discussed, and illustrated in the simplest terms to avoid unnecessary confusion and intimidation of readers who do not possess a physical science background.

A major criticism of this book is that it is written in a manner which is too simplistic for an anesthesiologist who has any technical background. In an attempt to be familiar to the practicing clinician, some of the illustrative examples suffer in precision. To explain diffusion, the authors state that "for example, if gas escapes from a broken gas pipe, the gas spreads by diffusion even after the gas tap has been turned off." Of course, diffusion is taking place, but the vast proportion of transport is most likely due to convection.

The authors state in the preface that their aim is to pro-

vide a link "between the level of teaching in school . . . and the more advanced textbooks on clinical physics." To this point they have also chosen to omit references and have kept mathematics to a minimum. In their effort to simplify, the authors have also incorporated inaccuracies into their text. For example, they define a venturi as a "steadily widening tube," which it is not, and further state that "the flow in such a tube remains laminar if the increase in cross-section is gradual." Although simplification of complex physics is necessary in a text such as this, oversimplification can lead to erroneous or misleading statements.

We feel the authors have achieved their stated goals, but we don't agree that these are goals for anesthesiologists. The older texts by Hill and MacIntosh are more precise and include detailed references (1,2). However, since MacIntosh's book is nearly 30 years old and the newest edition of Hill's book is dated 1980, some of the newer technologies are not included.

In summary, we feel the second edition of *Basic Physics and Measurement in Anesthesia* may be most appropriate for anesthesiologists with a nontechnical background who would like an easily readable survey of the subject.

Kevin K. Tremper, PhD, MD
Associate Professor and Chairman

Steven J. Barker, PhD, MD
Associate Professor
Department of Anesthesiology
University of California
Irvine Medical Center
Orange, CA 92668

References

1. MacIntosh R, Mushin WW, Epstein HG. *Physics for the Anaesthetist*. 2nd ed, Springfield, IL: Clark C. Thomas, 1958.
2. Hill EW. *Physics Applied to Anaesthesia*, 4th ed. London-Boston: Butterworths, 1980.

Isoflurane (Forane): A Compendium and Reference (second edition)

Edmond I. Eger II. Madison, WI: Anaquest, 1985, 160 pp.

Since the release of isoflurane for clinical use in 1981, it has become the most widely used volatile inhalation anesthetic agent in North America. There have been more than 20 million anesthetics given in which isoflurane was used. With this use comes an increased need for a concise yet scholarly text that can clearly yet succinctly delineate current knowledge available concerning this anesthetic agent. Though published by the drug manufacturer, the second edition of *Isoflurane* does fulfill this need.

As Professor Eger states in the preface, the first isoflurane compendium, published in 1981, contained data from patient, volunteer, and animal studies that comprised the isoflurane New Drug Application. The format of the second edition closely follows that of the first, but also thoroughly and accurately summarizes the many reports dealing with isoflurane that have been published during the four years

from 1981 to 1985. The chapter headings remain the same, except for the incorporation of the former chapters entitled "Malignant Hyperthermia" and "Intraocular Pressure" into Chapter 15—"Clinical Experiences with Isoflurane Administration."

When reading a text that is published by a pharmaceutical company, one wonders whether controversial issues will be avoided. In the *Isoflurane Compendium*, this is not the case. The limitations of isoflurane are thoroughly described, and controversial issues are discussed in detail. An example is the current controversy as to the occurrence of a "coronary steal" phenomenon when patients with coronary artery disease are anesthetized with isoflurane. The hypothesis is that isoflurane-related direct dilation of coronary arteries may divert blood flow to more normal vascular beds, away from coronary beds served by atherosclerotic vessels, resulting in ischemia. Eger gives a thorough presentation of the current literature for and against the hypothesis, without drawing a conclusion. In fact, none may be warranted at this time.

The physical presentation of the second edition is improved by a hard cover and a new typeset that improves readability of the text and the many tables and figures. The use of color and bold printing to offset subchapter headings and summaries is also an improvement. The most useful addition to the physical format of the compendium is that of an index, adding to its desirability as a reference volume.

Some of the valuable information that has been added to this edition includes the elucidation of Minimum Alveolar Concentration (MAC) values for isoflurane in infants and children. Also added are changes in solubility of isoflurane that take place with increasing age. There are also interesting references to the uptake of isoflurane by soda lime and the circle components, information not contained in the first edition.

The chapter entitled "Circulation" contains an expanded section on tachycardia, a common side effect of isoflurane, particularly in younger patients. There is an additional discussion of the "Mechanism for the Stability of Heart Rhythm with Isoflurane," as well as a discussion of interactions between beta and calcium blockers and isoflurane.

The chapter entitled "Neuromuscular Effects" has been updated to include discussions of interactions between isoflurane and the newer muscle relaxants vecuronium and atracurium. The latter two drugs seem to have differentiated enflurane as being more capable of enhancing neuromuscular blockade than isoflurane.

In this second edition of *Isoflurane*, Eger addresses not only the physiologic effects of the anesthetic but illuminates the implications of those effects to the anesthetist. All conclusions and observations in the text are made in relation to the alternatives available—halothane, enflurane, or intravenous agents. This is not just a textbook of isoflurane, but a comparative treatise about inhalation anesthetics and alternative anesthetic techniques.

In summary, the second edition of *Isoflurane* lives up to its title. It is a true compendium, a summary containing the essential information in a brief form—concise but comprehensive. It is a valuable addition to any anesthesiologist's

library. I measure the value of any textbook by how often I refer to it. Eger's first compendium has become well-thumbed. This second edition, in hard cover, should hold up better, and will get considerable use.

Judith B. Dillman, MD
Assistant Professor
Department of Anesthesia
University of Iowa
Iowa City, IA 52242

**Legal Issues in Transfusion Therapy:
Managing Risks in a Changing Environment**
Gilbert M. Clark, ed. Arlington, VA: American
Association of Blood Banks, 1986, 265 pp, \$20.00.

Whole blood or a fraction may be one anesthesiologist's most widely used nonanesthetic therapeutic agent. Blood products always seems to be available in adequate volumes, frequently on very short notice, and are usually taken for granted. Often they are given in anticipation of need. Anesthesiologists regularly share in the decision to start a transfusion and frequently make it without consulting the surgeon. Rarely are patients informed of any of the risks of blood product administration before a transfusion. In the light of these practices, it is well to query whether the administration of blood is really an unmixed blessing, and whether patients should be informed of the risks of a blood transfusion.

In the fall of 1985, the American Association of Blood Banks and the National Health Lawyers Association co-sponsored a two-day conference on the medical background and legal issues raised by the supplying and use of blood fractions. The faculty was made up of lawyers, physicians, physician-lawyers, and administrators. The transcribed proceedings of that conference and the handout material furnished to those who attended are combined in a paperback book that should help answer the queries posed above, as well as many others.

Subjects addressed include the organization of blood banking in this country; blood components and derivatives; transfusion complications, with ample coverage afforded to disease transmission; directed donations; donor consent and confidentiality; refusal to receive blood; the impact of AIDS on furnishing and prescribing blood products; and the economic and legal aspects of blood banking. Some of this material will be of little interest to those who prescribe blood products. Those who administer these potentially life-saving products regularly will, however, find much that will broaden their appreciation of the problems in blood banking, and of how those problems are solved to the enhancement of the quality of the final product.

At least seven chapters cover topics of specific interest to clinicians who prescribe or initiate blood product therapy. The first of these chapters details the various blood fractions that are currently available. In many instances a fraction, rather than whole blood, may be the therapy of choice. The current standard of care requires that anesthesia personnel be aware of which fraction to employ when one of the latter

may be preferable to whole blood. Three chapters and a portion of another contain material on complications. In spite of the best efforts of blood bank personnel, complications do occur. Having an awareness of potential complications will assist clinicians when discussing risks of anesthesia and operation with their patients. Should the risk of blood products be mentioned when obtaining informed consent? One of the speakers argues strongly that candidates for nonemergent operations should be warned of these risks if blood will or may be needed.

Of equal importance to obtaining the patient's consent and informed consent is the proper management of the patient who refuses blood. Competent patients do have a right to refuse any treatment under most circumstances. The publicity being given to the possibility of becoming infected with the AIDS virus by a transfusion will likely cause many patients to refuse to receive blood products in the future.

The chapter on directed donations may not appear to concern anesthesiologists. This reviewer came face to face with a policy against such donations during the illness of a loved one. Why should a healthy son not be permitted to make a directed donation to his mother? The book covers this subject, as well as a wealth of other material. I recommend the book very highly to all anesthesiologists, including trainees, and others who prescribe blood products. Perhaps after reading this material, blood products will no longer be taken for granted and will be placed in a different, more proper perspective among our armamentaria.

William H. L. Dornette, MD, JD
Department of Legal Medicine
Armed Forces Institute of Pathology
Washington, DC 20306

If the purpose is to present the most exhaustive recent review of the literature in one readable volume, accessible to medical professionals involved in perinatal care, the goal has been achieved. There are 21 chapters divided into six sections, giving authoritative reviews of 1) risks and pre-anesthetic evaluation, 2) maternal physiology and perinatal pharmacology, 3) analgesia and anesthesia for delivery, 4) major regional anesthesia, 5) maternal complications, and 6) the fetus and neonate. The new chapter considers anesthesia for surgical procedures during pregnancy, and its coauthors include the writers of a recent book on this subject.

On the whole, the style is remarkably uniform throughout, with a minimum of overlap of information, and the bibliography at the end of each chapter is up-to-date and complete. Although the principal editor's views and bias are apparent, this detracts only marginally from the overall presentation.

An added feature, which in this reviewer's opinion is not entirely successful, are the statements by invited experts dotted throughout the text. Representing very valid, but nonetheless personal opinions, these interjections flow sometimes with, and sometimes against, the text, so that the reader is required to suspend his or her attention at an inopportune moment in order not to miss a pithy nugget. Perhaps comments at the end of the chapter would have been more valuable. Nonetheless, this book should be read by all those involved in the complex issues involving the care of mother and baby.

Hilda Pedersen, MB, ChB, FFARCS
Associate Professor of Clinical Anesthesiology
Columbia University
New York, NY 10032

Anesthesia in Obstetrics: Maternal, Fetal, and Neonatal Aspects

G. A. Albright, J. E. Ferguson II, and T. H. Joyce III, eds.
Stoneham, MA: Butterworths, 1986, 622 pp, \$69.95.

The revision and updating of medical texts has become the task of Sisyphus. No sooner has the definitive chapter appeared in publication, than another is being planned to avoid obsolescence. Here we have an extensively expanded edition of the 1978 volume, in which Dr. Albright has received the cooperation of a number of other distinguished authors and has introduced a comprehensive amount of new material, including an added chapter.

Books Received

Receipt of the following books from their publishers is acknowledged with thanks. Selected books from this list will be reviewed in the future.

King M, ed. *Primary Anaesthesia*. New York: Oxford University Press, 1986, 169 pp, \$13.95 (pages bound).

Kirby RR, Taylor RW, eds. *Respiratory Failure*. Chicago: Yearbook Medical Publishers, 1986, 665 pp, \$75.00.

Miller RD, Kirby RR, Ostheimer GW, Saidman LS, Stoelting RIC. *1986 Yearbook of Anesthesia*. Chicago: Yearbook Medical Publishers, 1986, 387 pp, \$44.95.

Murray JF. *The Normal Lung, 2nd edition*. Philadelphia: WB Saunders Company, 1986, 377 pp, \$27.95.

Raj PP, ed. *Practical Management of Pain*. Chicago: Yearbook Medical Publishers, 1986, 956 pp, \$125.00.

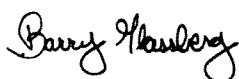
Guest Reviewers for 1986

Dr. Hassan Ali
Dr. Truett Allison
Dr. Peter L. Bailey
Dr. Charlotte Bell
Dr. Leonard Brand
Dr. Harold Breivik
Dr. Hugh A. Brown
Dr. Robert Byck
Dr. C. Callander
Dr. Enrico M. Camporesi
Dr. Daniel B. Carr
Dr. Frank Cervencko
Dr. Theodore G. Cheek
Dr. David A. Cherry
Dr. Norman J. Clark
Dr. Fiona M. Clements
Dr. John Crowhurst
Dr. Sanjay Datta
Dr. Richard Davis
Dr. Norbert P. de Bruijn
Dr. Daniel F. Dedrick
Dr. Robert H. Dworkin
Dr. Nabil Fahmy
Dr. Ronald J. Faust
Dr. Hugh L. Flanagan, Jr.
Dr. Paolo Flezzani
Dr. John Fox
Dr. Thomas J. Gal
Dr. Alex Gallus
Dr. Simon Gelman
Dr. C. Norman Gillis
Dr. Aaron J. Gissen
Dr. Peter S. A. Glass
Dr. Michael S. Gorback
Dr. Nishan G. Goudsouzian
Dr. G. K. Gourlay
Dr. William J. Greeley
Dr. Jeffrey Gross
Dr. Lavern D. Gugino
Dr. Bradford D. Hare
Dr. Russell F. Hill
Dr. Carol A. Hirshman
Dr. Anton Hole

Dr. Jan Charles Horrow
Dr. Heather E. Hosie
Dr. Robert J. Hudson
Dr. Anthony H. Isley
Dr. Kham Jhamandas
Dr. David R. Jobes
Dr. R. W. Johnson
Dr. Robert W. Katayjian
Dr. Robert A. Kates
Dr. Lee A. Kearse, Jr.
Dr. Sean K. Kennedy
Dr. Greg Koski
Dr. Carol L. Lake
Dr. Donald H. Lambert
Dr. David E. Leith
Dr. Peter E. Lillie
Dr. Leonard J. Lind
Dr. R. W. McIntyre
Dr. Rosemarie Maddi
Dr. Jonathan B. Mark
Dr. Bryan Marshall
Dr. Terry Massagee
Dr. Laurence E. Mather
Dr. Richard Matteo
Dr. Marshall Millman
Dr. Brian Milne
Dr. Emerson A. Moffitt
Dr. Richard Moon
Dr. Richard W. Morris
Dr. Stanley A. Muravchick
Dr. Craig Nancarrow
Dr. Shih-Hsun Ngai
Dr. T. E. Nicholas
Dr. Susan C. Nicholson
Dr. Eugene Ornstein
Dr. Nathan L. Pace
Dr. David Paly
Dr. Eugene J. Pantuck
Dr. John E. Peacock
Dr. Hilda Pedersen
Dr. Beverley K. Philip
Dr. James H. Philip
Dr. John L. Plummer

Dr. Timothy J. Quill
Dr. Morton K. Raeder
Dr. Steven Raymond
Dr. Lloyd F. Redick
Dr. C. S. Reilly
Dr. Gilbert Ritchie
Dr. John G. Roberts
Dr. Carl E. Rosow
Dr. Peter Rothstein
Dr. David J. Rowbotham
Dr. John Rowlingson
Dr. W. J. Russell
Dr. John Savarese
Dr. H. G. Schroeder
Dr. Dianne L. Scott
Dr. Peter S. Sebel
Dr. Derrick G. Selby
Dr. D. H. Short
Dr. Dana L. Simon
Dr. George Skowronski
Dr. James M. Sloan
Dr. Theodore C. Smith
Dr. Richard A. Steinbrook
Dr. Joseph A. Stirt
Dr. Gilbert Stone
Dr. Gary R. Strichartz
Dr. George P. Topulos
Dr. Lubos Triner
Dr. G. T. Tucker
Dr. Bruno J. Urban
Dr. Alnis Vedig
Dr. Alan Wald
Dr. Josef K. Wang
Dr. David S. Warner
Dr. David S. Warren
Dr. Walter L. Way
Dr. Charles Weissman
Dr. Gerry Weston
Dr. N. B. Williams
Dr. Richard J. Willis
Dr. Roger Wilson
Dr. Peter Yellowlees
Dr. Guy Zimmerman

STATEMENT OF OWNERSHIP, MANAGEMENT, AND CIRCULATION (Required by 39 U.S.C. 3685). 1. Title of publication: Anesthesia and Analgesia. B. Publication no.: 00032999. 2. Date of filing: 10/1/86. 3. Frequency of issue: Monthly. A. No. of issues published annually: 12. B. Annual subscription price: \$95.00. 4. Location of known office of publication: 52 Vanderbilt Avenue, New York, NY 10017. 5. Location of the headquarters or general business offices of the publishers: 52 Vanderbilt Avenue, New York, NY 10017. 6. Names and complete addresses of publisher, editor, and managing editor: Publisher, International Anesthesia Research Society, 3645 Warrensville Center Road, Cleveland, OH 44122; Editor, Nicholas M. Greene, MD, Yale University, New Haven, CT 06510. Managing Editor: Amy R. Segal, 52 Vanderbilt Avenue, New York, NY 10017. 7. Owner: International Anesthesia Research Society, 3645 Warrensville Center Road, Cleveland, OH 44122. 8. Known bondholders, mortgagees, and other security holders owning or holding 1 percent or more of the total amount of bonds, mortgages, or other securities: None. 9. The purpose, function, and nonprofit status of this organization and the exempt status for Federal income tax purposes have not changed during preceding 12 months. 10. Extent and nature of circulation. A. Total no. copies printed (net press run): Average no. copies each issue during preceding 12 months, 20,981; actual no. copies of single issue published nearest to filing date, 20,394. B. Paid circulation. 1. Sales through dealers and carriers, street vendors, and counter sales: None. 2. Mail subscription: Average no. copies each issue during preceding 12 months, 17,162; actual no. copies of single issue published nearest to filing date 17,493. C. Total paid circulation: Average no. copies each issue preceding 12 months, 17,162; actual no. copies of single issue published nearest to filing date 17,493. D. Free distribution by mail, carrier or other means, samples, complimentary, and other free copies: Average no. copies each issue during preceding 12 months, 289; actual no. copies of single issue published nearest to filing date, 289. E. Total distribution: Average no. copies each issue during preceding 12 months, 17,451; actual no. copies of single issue published nearest to filing date, 17,782. F. Copies not distributed. 1. Office use, left over, unaccounted, spoiled after printing: Average no. copies each issue during preceding 12 months, 3530; actual no. copies of single issue published nearest to filing date, 2612. 2. Return from news agents: None. G. Total: Average no. copies each issue during preceding 12 months, 20,981; actual no. copies of single issue published nearest to filing date, 20,394. 11. I certify that the statements made by me above are correct and complete.



Barry Glassberg
Fulfillment Manager



Anesthesia and Analgesia

Annual Index Volume 65, 1986

BOARD OF TRUSTEES

International Anesthesia Research Society

Dean H. Morrow, MD, *Chairman*
Bruce F. Cullen, MD, *Vice Chairman*
Emerson A. Moffitt, MD, *Executive Secretary*
Douglas B. Craig, MD
E. Paul Didier, MD
Judith H. Donegan, MD, PhD
Noel W. Lawson, MD
John T. Martin, MD
Robert K. Stoelting, MD
John L. Waller, MD
Paul R. Dumke, MD, *Emeritus Trustee*
Morris J. Nicholson, MD, *Emeritus Trustee*
B. B. Sankey, MD, *Emeritus Trustee*
T. H. Seldon, MD, *Emeritus Trustee*

EDITORIAL BOARD

Anesthesia and Analgesia

Editor in Chief
Nicholas M. Greene, MD

Editors
David R. Bevan, MA, MD, BChir
D. Ryan Cook, MD
Benjamin G. Covino, MD
Norig Ellison, MD
Mieczyslaw Finster, MD
Alison B. Froese, MD
Edward D. Miller Jr, MD
Walter S. Nimmo, MD, BSc, FRCP, FFARCS
Daniel M. Philbin, MD
J. Gerald Reves, MD
Petter A. Steen, MD
John H. Tinker, MD
K. C. Wong, MD, PhD

Book Review Editor
Norig Ellison, MD

Author Index

- Aaron D, see Casthely PA
 Abboud TK, see Murakawa K
 Abdulatif M, see Naguib M
 Abel MD, Nishimura RA, Callahan MJ, Tajik AJ. Intraoperative left ventricular wall motion—transesophageal 2-D echocardiographic image analysis (abstract) S1
 see Weinlander CM
 Abouleish E. Postpartum tubal ligation requires more bupivacaine for spinal anesthesia than does cesarean section 897
 Uterine displacement device (letter) 424
 Abraham EC, Gold MI, Herrington CA. A comparison of propofol, thiopental and methohexital as induction agents (abstract) S2
 Abrams L, see Casthely PA
 Absoud GH, see Naguib M
 Acharya PA, see Nicoll JMV
 Adams ML, see Henling CE
 see Samuelson PN
 Addonizio VP, see Guffin AV
 see LaMantia KR
 Adelhof B, see Petring OU
 Adenwala J, see Younker D
 Adler E, Gibbons PA, Striker TW, Denson DD. Ketamine: an alternative for the anesthetic management of acute epiglottitis (abstract) S3
 Agoston S, see Bencini AF
 see Meistelman C
 see Schwarz S
 see Sohn YJ
 Ahlen K, see Nicoll JMV
 Ahmad I, see Norman EA
 Ahn H, see Toung TJK
 Alano J, see Toung TJK
 Albin T, see Goroszeniuk T
 Albrecht RF, see Becker GL
 see Hoffman WE
 Alcover I, see Henning RJ
 Aldrete JA, Castillo RA, Bradley EL Jr. Changes of fresh gas flow affect the tidal volume delivered by anesthesia ventilators (abstract) S4
 Alexander GD, see Kunjappan VE
 Ali HH, see deBros FM
 see Goldhill DR
 see Scott RPF
 Alifimoff JK, see Navalgund AA
 Allen GC. Vecuronium and malignant hyperthermia (letter) 212
 Allen ML, see Feldstein GS
 see Waldman SD
 Allen PD, Walman T, Concepcion M, Sheskey M, Patterson MK, Cullen D, Covino BG. Epidural morphine provides postoperative pain relief in peripheral vascular and orthopedic surgical patients: a dose-response study 65
 Alpert CC, Cooke JE. Extending the life of oximetry monitoring probes (letter) 826
 Althaus JS, Miller ED Jr, DiFazio CA, Moscicki JC, Engle JS. Further evidence for central 5-HT participation in sufentanil-reduced MAC (abstract) S5
 see Lynch C III
 Anderson ST, Barker SJ. Temperature correction of blood gas tensions? (letter) 420
 Appel P, see Lippmann M
 Arai T, Hatano Y, Ishida H, Mori K. Use of nicardipine in the anesthetic management of pheochromocytoma 706
 Arakawa K, see Kim J-M
 Arismendy J, see Grant G
 Armstrong PJ, Bersten A. Normeperidine toxicity 536
 Arnold WP, see Ross WT
 Arthur GR, see Rothstein P
 Artru AA. Partial preservation of cerebral vascular responsiveness to hypocapnia during isoflurane-induced hypotension in dogs 660; (abstract) S6
 Colley PS. Bunegin-albin CVP catheter improves resuscitation from lethal venous air embolism in dogs (abstract) S7
 Hui GS. Physostigmine reversal of general anesthesia for intraoperative neurologic testing: associated EEG changes 1059
 Arvieux CC, see Ramsay JG
 Askanazi J, see Damask MC
 Athanasiadis C, see Mastrocostopoulos G
 Atlee JL, Brownlee SW. Thiopental and epinephrine-induced ventricular arrhythmias with enflurane or isoflurane in dogs (abstract) S8
 Atlee JL III, Roberts FL. Thiopental and epinephrine-induced dysrhythmias in dogs anesthetized with enflurane or isoflurane 437
 Audenaert SM, see Finholt EA
 Avram MJ, Shanks CA, Ronai AK, Fragen MP. Metocurine administration by combined bolus and infusion (abstract) S9
 see Shanks CA
 Axelsson KH, Sundberg AEA, Edström HH, Widman GB, Sjöstrand UH. Venous blood concentrations after subarachnoid administration of bupivacaine 753
 Azad SS, Maguire D, Goldberg ME. Junctional rhythm can mimic air embolism during precordial Doppler monitoring 1083
 Azar I, see Thiagarajah S
 Badrinath S, Vazeery AK, Ivankovich A. Effect of vecuronium on intraocular pressure (abstract) S10
 Bailey PL, Clark NJ, Pace NL, Isern M, Stanley TH. Failure of nalbuphine to antagonize morphine: a double blind comparison with naloxone 605
 see Mock DL
 Baldeck AM. Labat's regional anesthesia techniques and clinical application (book review) 428
 Baldwin CC, see Neuman GG
 Banner TE, see Schultetus RR
 Banning A-M, Schmidt JF, Chræmer-Jorgensen B, Risbo A. Comparison of oral controlled release morphine and epidural morphine in the management of postoperative pain 385
 Bansinath M, see Ramabadrana K
 Baraka A. Transtracheal jet ventilation during fiberoptic intubation under general anesthesia (letter) 1091
 Mansour R, Jaoudé CA, Muallem M, Hatem J, Jaraki K. Entrainment of oxygen and halothane during jet ventilation in patients undergoing excision of tracheal and bronchial tumors 191
 Muallem M, Karam H. Succinylcholine triggered masseter spasm in a patient with trigeminal nerve palsy (letter) 1245
 Usta N. Verapamil treatment of intractable reperfusion ventricular tachycardia/fibrillation (letter) 102
 Barash P, see Biondi J
 see Hines RL
 see Moleski R
 see Smith G
 Barker RA, see Moffitt EA
 Barker SJ, Tremper KK. A new look at pressure loss through endotracheal tubes: RAE and CAT tubes (abstract) S11
 Tremper KK, Gamel DM. A clinical comparison of transcutaneous Po and pulse oximetry in the operating room 805
 Tremper KK, Hufstetler S, Hyatt J, Zaccari J. The effects of carbon monoxide inhalation on

- noninvasive oxygen monitoring (abstract) S12
see Anderson ST
see Tremper KK
- Barth A, see Damask MC
- Barton C, see Williams L
- Basora J, see Martin R
- Basta SJ, see Scott RPF
- Bates JN, see Chestnut DH
- Batson AG, see deBros FM
- Baumgärtner WA, see McGarrigle RE
- Bause GS, Black RG. Anesthesiologist's back: epidemiology of a major occupational disease (abstract) S13
- Baxter A, see Penning JP
- Baydur A, Sassoon CSH, Stiles CM.
Active inspiratory impedance and load compensation: effects of duration of anesthesia 1
- Baysinger CL, Menk EJ, Harte E, Middaugh R. The successful treatment of dural puncture headache after failed epidural blood patch 1242
- Schmidt SI. Injectable confusion (letter) 104
- Beamer WC, see Prough DS
- Beatty PCW, see Bolder PM
- Becker GL. Halothane effects on synaptosomal acetylcholine metabolism (letter) 103
- Miletich DJ, Albrecht RF. Effects of halothane and decreased PO_2 on high energy phosphate levels maintained by isolated rat liver mitochondria 1130
- Pelligrino DA, Miletich DJ, Albrecht RF. The effects of nitrous oxide on oxygen consumption by isolated cerebral cortex mitochondria 355
- Bedder MD, Kozody R, Palahniuk RJ, Cumming MO, Pucci WR. Clonidine prolongs tetracaine spinal anesthesia in dogs (abstract) S14
- Bedford RF, see Minton MD
- Behbehani MM, see Thomas RD
- Belani KG, see Liao JC
- Bell JG, see Su JY
- Bellefleur M, Berman LS. Factors affecting gas entrainment with high-frequency jet ventilation (abstract) S15
- Belusko R, see Kleinman B
- Bencini AF, Scaf AHJ, Sohn YJ, Meistelman C, Lienhart A, Kersten UW, Schwarz S, Agoston S. Disposition and urinary excretion of vecuronium bromide in anesthetized patients with normal renal function or renal failure 245
see Meistelman C
see Sohn YJ
- Bennett HL, Boyle WA. Selective remembering: anesthesia and memory (letter) 988
- Benson KT, see Kim J-M
- Benthuyssen JL, see Smith NT
- Benzon HT, Toleikis JR, Shanks C, Ramseur A, Sloan T. Lidocaine ulnar nerve blocks alter SSEP responses (abstract) S16
- Toleikis JR, Shanks C, Ramseur A, Sloan T. Somatosensory evoked potential quantification of ulnar nerve blockade 843
- Berg J, see Triantafillou AN
- Berger JJ, Pyles ST, Saga-Rumley SA. Does topical anesthesia of the sphenopalatine ganglion with cocaine or lidocaine relieve low back pain? 700; (abstract) S17
- Berman LS, see Bellefleur M
see Schultetus RR
- Bernard JM, see Fusciardi J
- Bernstein JL, see Eisenkraft JB
- Berrizbeitia LD, see Butterworth JF IV
- Bersten A, see Armstrong PJ
- Bertrand M, see Fusciardi J
- Bevan DR. Acid-base regulation and body temperature (book review) 997
- Biber B, see Schaefer CF
- Bigler D, see Hjortso N-C
- Biondi J, Hines R, Matthay RA, Barash P. Comparative right ventricular function during assist control, intermittent mandatory and spontaneous ventilation (abstract) S18
- Hines R, Rafferty T, Rogol P, Scott W, Barash P. The effect of high frequency positive pressure ventilation on right and left ventricular function 679
- Birmingham PK, Cheney FW, Ward RJ. Esophageal intubation: a review of detection techniques 886
- Bishop MJ, see Stout D
- Black RG, see Bause GS
- Blaise GA, McMichan JC, Nugent M, Hollier LH. Nalbuphine produces side effects while reversing narcotic-induced respiratory depression (abstract) S19
- Blanck TJJ, see McGarrigle RE
- Bledsoe SW, see Townes BD
- Bleyaert AL, see Navalgund AA
- Blomberg R. The dorsomedian connective tissue band in the lumbar epidural space of humans: an anatomical study using epiduroscopy in autopsy cases 747
- Bloor BC, Finander LS, Flacke WE, Van Etten A. Effect of clonidine on sympathoadrenal response during sodium nitroprusside hypotension 469
- Blyden GT, see Greenblatt DJ
- Boaden RW, see Grosslight KR
- Bohman BK, see Northrip DR
- Bolder AR, see Bolder PM
- Bolder PM. Post lumbar puncture headache in pediatric oncology patients (abstract) S21
- Healy TEJ, Bolder AR, Beatty PCW, Kay B. The extra work of breathing through adult endotracheal tubes 853
- Bolding WR, see DiFazio CA
- Boriath K, see Chrusasik J
- Bonnet F, see Chauvin M
- Borland LM. The manual of pediatric anesthesia (book review) 108
- Bose D, see Ong BY
- Bosnjak ZJ, Murthy VS, Dujic Z, Hwang TF, Kampine JP. Effects of chronic administration of verapamil on cardiac electrophysiology in the rabbit (abstract) S22
- Stowe DF, Kampine JP. Comparison of lidocaine and bupivacaine depression of sinoatrial node activity during hypoxia and acidosis in adult and neonatal guinea pigs 911
- Bottorff M, see Ramanathan J
- Bousseau D, see Coriat P
- Bovill JG, see Van Rheineck Leyssius AT
- Bowman RE, see Levin ED
- Boyle WA, see Bennett HL
- Brackett DJ, see Schaefer CF
- Bradley EL, see Castillo R
see Henling CE
- Bradley EL Jr, see Aldrete JA
see Castillo RA
see Ebert J
see Jebeles JA
see Kissin I
see Samuelson PN
- Bramwell RS, see Newsome LR
- Brandford HG, see Lynn AM
- Brandom RW. GASMAN—understanding anesthesia uptake and distribution (book review) 107
- Braunstein M, see Reitan JA
- Braverman B, Ivankovich AD, Woronowicz A. Cardiovascular effects of atracurium and vecuronium on digitalized dogs (abstract) S23
- Breen PH, Sznajder JI, Morrison P, Hatch D, Wood LDH, Craig DB. Constant flow ventilation in anesthetized patients: efficacy and safety. 1161
- Brichtant JF, Rouby JJ, Viars P. Intermittent positive pressure ventilation with either positive end-expiratory pressure or high frequency jet ventilation (HFJV) or HFJV alone in human acute respiratory failure 1135
- Bridenbaugh PO, Hagenouw RRP, M,

- Gielen MJM, Edström HH. Addition of glucose to bupivacaine in spinal anesthesia increases incidence of tourniquet pain 1181
see Hagenouw RRP
see Thompson GA
- Britt BA, Scott EA. Failure of the platelet-halothane nucleotide depletion test as a diagnostic or screening test for malignant hyperthermia 171
- Britt BA, Scott EA, Klaiman A, Jones P, Steward DJ. Failure of the tourniquet-twitch test as a diagnostic or screening test for malignant hyperthermia 1047
- Broad Y, see Sosis M
- Brock-Utne JG, see Ivankovich AD
- Brodsky JB, see Wakerlin G
- Brown BR Jr, see Lind RC
- Brown EM. Regional anesthesia and clinical applications (book review) 216
see Kunjappan VE
- Brown M. 1985 Yearbook of critical care medicine (book review) 430
- Brown SC, see Lam AM
- Brownlee SW, see Atlee JL
- Bruce DL, Norman P. Fentanyl and fertilization; reply (letter) 103
- Brundage DM, see Koehntop DE
- Bruni CY, see Fauss BG
- Brussel T, see Van Aken H
- Brynes R, see Zaidan JR
- Buchea OC, see Kapur PA
- Buckley JJ, see Koehntop DE
see Liao JC
- Buhl RW, see Freye E
- Burgoyne R, see Enhorning G
- Burke D. Diazepam and free plasma bupivacaine concentration (letter) 314
- Burm AGL, Van Kleef JW, Gladines MPRR, Olthof G, Spierdijk J. Epidural anesthesia with lidocaine and bupivacaine: effects of epinephrine on the plasma concentration profiles 1281
- Burney RG. Acute pain (book review) 214
- Burrows FA, see James PD
- Bursztein S, see Levin H
- Butterworth JF IV, Piccione W Jr, Berrizbeitia LD, Dance G, Shemin RJ, Cohn LH. Augmentation of venous return by adrenergic agonists during spinal anesthesia 612
- Callahan MJ, see Abel MD
- Campos JH, Kapur PA. Coronary hemodynamic effects of nifedipine during isoflurane anesthesia in the dog (abstract) S24
see Kapur PA
- Camu F, see Gepts E
- Cane RD, see Greene SJ
- Cannon JE, Fahey MR, Castagnoli KP, Furuta T, Sharma M, Miller RD. The effect of different anesthetics on a continuous vecuronium infusion (abstract) S23
- Capan LM, see Vaida GT
- Caplan RA, Su JY. Interaction of halothane and verapamil in isolated papillary muscle 463
- Carapetis RJ, see Mather LE
- Carbone-Traber KB, Shanks CA. Glass particle contamination in single-dose ampules 1361
- Carlson EB, see Kates RA
- Carlson SA, see Leicht CH
- Carlvin AO, see Kimovec MA
see Koht A
- Carpenter RL, Eger EI II, Johnson BH, Unadkat JD, Sheiner LB. Effect of anesthetic duration on inhaled anesthetic pharmacokinetics (abstract) S26
- Eger EI II, Johnson BH, Unadkat JD, Sheiner LB. Pharmacokinetics of inhaled anesthetics in humans: measurements during and after the simultaneous administration of enflurane, halothane, isoflurane, methoxyflurane, and nitrous oxide 575
- Carroll SK, see Ebert J
- Carron H, see DiFazio CA
- Casella JF, see Wetzel RC
- Castagnoli KP, see Cannon JE
- Casthely PA, Goodman K, Fyman PN, Abrams LM, Aaron D. Hemodynamic changes after the administration of protamine 78
- Goodman K, Fyman PN, Abrams L, Aaron D. Hemodynamic changes and histamine release following administration of protamine, via a central vein or peripheral or left atrium: a comparative study S27
- Jabons M, Griep RB, Ergin MA, Goodman K. Ketanserin in the preoperative and intraoperative management of a patient with carcinoid tumor undergoing tricuspid valve replacement 809
see Fyman PN
- Castillo R, Kissin I, Bradley EL. Selective kappa opioid agonist for spinal analgesia without the risk of respiratory depression 350
- Kisson I, Bradley EL Jr. Opioid agonist for spinal analgesia without risk of respiratory depression (abstract) S28
see Aldrete JA
- Cervenko FW. Prolonged QT interval syndromes (letter) 212
- Chang KSK, see Graham TM
- Chang WJ, see Matteo RS
- Chang-hyon Y, see Kuhnert BR
- Charney J, see Lippmann M
- Chauhan D, see Ramanathan J
- Chauvin M, Bonnet F, Montebault C, Levron JC, Viars P. The influence of hepatic plasma flow on alfentanil plasma concentration plateaus achieved with an infusion model in humans: measurement of alfentanil hepatic extraction coefficient 999
- Chelly J, see Hysing ES
- Chen CT, see Toung TJK
- Chen LH, see Kambam JR
- Chen WS, see Mok MS
see Tsai SK
- Cheney FW, see Birmingham PK
- Cheng EY, Renschler MF, Mihm FG, Sladen RN, Rosenthal MH. Noninvasive respiratory monitoring of patients during weaning from mechanical respiratory support (abstract) S29
- Chestnut DH, Bates JN, Choi WW. Continuous infusion epidural analgesia with lidocaine: influence on the second stage of labor (abstract) S30
- Choi WW, see Chestnut DH
see Mehta MP
- Chræmmer-Jorgensen B, Hoilund-Carlson PF, Marving J, Christensen V. Lack of effect of intravenous lidocaine on hemodynamic responses to rapid sequence induction of general anesthesia: a double-blind controlled clinical trial 1037
see Banning A-M
- Christensen V, see Chraemmer-Jorgensen B
- Chrubasik J, Bonath K. CSF morphine concentrations after administration of sustained release morphine per os and morphine-HCl IM in dogs (abstract) S31
- Chung DC, Kerr CR. Termination of atrial flutter in postoperative cardiac surgical patients by transesophageal pacing (abstract) S32
- Ciamelli F, see Freye E
- Cierpka H, Fahmy NR. Bis-trimethaphan nitroprusside (TNP): a new more potent "nitroprusside" (abstract) S33
- Citrin A, see Younker D
- Claeys DW. Monitoring inspired oxygen concentrations in nonbreathing systems (letter) 1248
- Clark DL, see Moore RA
- Clark NJ, see Bailey PL
see Streisand JB
- Clark RE, see Nancherla AR
- Coburn CM, Eger EI II. The partial pressure of isoflurane or halothane does not affect their solubility in

- blood: inhaled anesthetics obey Henry's law 672
- Eger EI II. The partial pressure of isoflurane or halothane does not affect their solubility in rabbit blood or brain or human brain: inhaled anesthetics obey Henry's law 960
- Cohen E, Thys DM, Eisenkraft JB, Kirschner PA, Kaplan JA. Monitoring of mixed venous oxygen saturation as an indicator of oxygenation during thoracic surgery (abstract) 534
- Cohen JA, Denisco RA, Richards TS, Staples ED, Roberts AJ. Hazardous placement of a Robertshaw-type endobronchial tube 100
- Cohen M, see Duncan PG
see Eisenkraft JB
- Cohen SE, see Tan S
- Cohn LH, see Butterworth JF IV
- Colley PS, see Artru AA
- Collins JG. Effects of ketamine on low intensity tactile sensory input are not dependent upon a spinal site of action 1123
see Matsumoto M
- Colliver JA, Manchikanti L. Acid aspiration risk factors; reply (letter) 210
see Manchikanti L
- Concepcion M, see Allen PD
see Datta S
- Conley RJ. Scavenging of capnometers (letter) 102
- Conroi PT. Anaesthetic equipment: physical principles and maintenance (book review) 1255
- Contreras J, see Lam AM
- Cook DR. The pharmacological basis of therapeutics (book review) 1253
- Stiller R, Ingram M. In vitro degradation of atracurium (letter) 543
see Schieber RA
- Cook JM, see Hoffman WE
- Cooke JE, see Alpert CC
- Coombs DW. Epidural phenol neurolysis using daily needle placements; reply (letter) 822
- Cooperman LH. Classical anesthesia files (book review) 429
- Effects of anesthesia (book review) 323
- Cope DK, Miller JN. Local and spinal anesthesia for cesarean section in a patient with myotonic dystrophy 687
- Coriat P, Mundler O, Bousseau D, Fauchet M, Rous AC, Echter E, Viars P. Response of left ventricular ejection fraction to recovery from general anesthesia: measurement by gated radionuclide angiography 593
- Cork RC, Gallo JA, Otto CW, Emery RW. The effect of early extubation on shunt after coronary artery bypass (abstract) 535
see Gallo JA
see James MF 4
- Cosimi AB, see deBros FM
- Coudere E, see Marty J
- Coursin DB. Invasive procedures in critical care (book review) 1371
- Cousins CL, see Imrie DD
- Cousins MJ. Textbook of pain (book review) 5-8
see Lunam CA
- Couture LJ, Stozy S, Edmonds HL Jr. EMG response to auditory stimuli under isoflurane anesthesia (abstract) 536
see Stolzy S
- Covino BG, see Allen PD
see Rothstein P
- Coyle DE, see Denson DD
see Thomas ED
- Cozanitis DA, Kaloheimo MPJ. Operating room pollution from "capnographs" (letter) 990
- Craig DB, see Green PH
- Crampton RS, see Lake CL
- Cremonesi E, Murata KN. Infiltration of a neuromuscular relaxant in diagnosis and treatment of torticollis 1077
- Croughwell NE, see Flezzani P
- Cruz JC. Reducing the cost of using neuromuscular relaxants (letter) 315
- Crystal GJ, Salem MR. Chemoreflex hypoxemia causes non-uniform antagonism of hypoxic vasodilation in canine brain (abstract) 537
- Salem MR. Myocardial oxygenation during selective graded coronary hemodilution in the working canine heart (abstract) 538
- Csömör S Jr, see Hamar O
- Cullen BF, see Stout D
- Cullen D, see Allen PD
see Hilavacek JR
- Cumming MC, see Bedder MD
- Curling PE, see Newsome LR
- Dalens B, Taniguchi A, Haberer J-P. Lumbar epidural anesthesia for operative and postoperative pain relief in infants and young children 1069
- Damask MC, Weissman C, Barth A, Todd G, Askanaazi J, Rosenbaum SH. General vs epidural—which is the better anesthetic technique for femoral-popliteal bypass surgery? (abstract) 539
- Dance G, see Butterworth JF IV
- Daniels D, Rosen MA. A method for monitoring pulse rate changes during test doses of epidural anesthetic solutions in obstetrics (letter) 1089
- Datta S, Hurley RJ, Naulty JS, Stern P, Lambert DH, Concepcion M, Tulchinsky D, Weiss JB, Ostheimer GW. Plasma and cerebrospinal fluid progesterone concentrations in pregnant and nonpregnant women 950
- Dau PC, see Vender JS
- Dauchot PJ, see Furgerson CL
- Davidson JT, see Perel A
- Davis J, see Mills C
- Davis N, see Peterson DR
- Davis RF. The effect of isoflurane on myocardial ischemia in dogs during coronary artery occlusion (abstract) 540
DeBoer LWV, Maroko PR. Thoracic epidural anesthesia reduces myocardial infarct size after coronary artery occlusion in dogs 711
see Frank LP
- de Jong P, see Streisand JB
- de la M. Hall P, see Lunam CA
- de Rosayro AM, see Wilton NCT
- de Vries C, see Streisand JB
- De Wolf AM. Erroneous blood pressure readings during and after IMA dissection for CABG surgery (letter) 827
- DeBoer GE, see Ebrahim ZY
- DeBoer LWV, see Davis RF
- deBros FM, Lai A, Scott R, deBros J, Batson AG, Goudsouzian N, Ali HH, Cosimi AB, Savarese JJ. Pharmacokinetics and pharmacodynamics of atracurium during isoflurane anesthesia in normal and anephric patients 743
- deBros J, see deBros FM
- Dec-Silver H, see Sanford TJ Jr
see Smith NT
- DelCampo C, see Moffitt EA
- Delphin E, see Smerling A
- Denis R, Letourneau J, Londorf D. Psychomotor tasks and recovery from anesthesia; reply (letter) 544
- Denisco RA, see Cohen JA
- Dennett JE, see James MFM
- Denson DD, Myers JA, Thompson GA, Coyle DE. Diazepam and free plasma bupivacaine concentration; reply (letter) 314
see Adler E
see Thomas RD
see Thompson GA
- Desmonts JM, see Marty J
- Dharamraj CM, see Schultetus RR
- DiFazio CA, Carron H, Grosslight KR, Moscicki JC, Bolding WR, Johns RA. Comparison of pH-adjusted

- lidocaine solutions for epidural anesthesia 760
see Althaus JS
see Finholt DA
- DiNardo JA, Satwicz PR. Nonlinear relationship of arterial to peak end tidal partial pressure of CO₂ during CASG surgery (abstract) S41
- DiSesa V, see Mark JB
- Diamond C, see Lam AM
- Diaz J, see Silverberg PA
- Didier EP. High-frequency ventilation in intensive care and during surgery (book review) 215
- Dikmen SS, see Townes BD
- Dillman JB. Isoflurane (Forane): a compendium and reference (book review) 1372
- Dohi S, Takeshima R, Naito H. Ventilatory and circulatory responses to carbon dioxide and high level sympathectomy induced by epidural blockade in awake humans 9
see Ishizawa Y
see Matsumiya N
- Dolman J, see Silvay G
- Domer P, see Samra SK
- Donham RT, see Toung JTK
- Dornette WHL. Legal issues in transfusion therapy: managing risks in a changing environment (book review) 1373
- Doursout M-F, see Hysing ES
- Downs JB, see Stock MC
- Doze VA, Westphal LM, White PF. Comparison of propofol with methohexital for outpatient anesthesia 1189
- Draxler VH, see Spiss CK
- Drefeldt B, see Fletcher R
- Drexler H, Feldman B, Finsterbusch A, Pogrund H, Rousso M. Low-dose intravenous regional anesthesia in a case of multistaged bilateral hand surgery 812
- Drummond GB, Logan MR. Position and spread of spinal anesthetic solutions (letter) 314
- Drummond JC, see Scheller MS
see Schubert A
see Sohn YJ
- Du Toit PS, see Thorburn JR
- Dujic Z, see Bosnjak ZJ
- Duncan PG, Cohen M. Anaesthetic morbidity: factors of clinical significance (abstract) S42
- Dundee JW, Halliday NJ, Harper KW. Midazolam as an intravenous induction agent in the elderly (letter) 1089
- McCollum JSC, Robinson FP, Halliday NJ. Elderly patients are unduly sensitive to propofol (abstract) S43
see Moore J
see Wilson CM
- Durant PAC, Yaksh TL. Distribution in cerebrospinal fluid, blood, and lymph of epidurally injected morphine and inulin in dogs 583
- Durbin CG Jr, see Lynch C III
- Dursztman M, see Grant G
- Dwersteg J, see Stout D
- Dworacek B, see Ruprecht J
- Dzelzkalns RR, see Mock DL
- Earls F, see Garfield JM
- Ebert J, Carroll SK, Bradley EL Jr. Closed-loop feedback control of muscle relaxation with vecuronium in surgical patients (abstract) S44
Harris C, Pearson J, Gelman S, Bradley EL Jr. Comparison of the protective effects of esmolol and fentanyl during laryngoscopy (abstract) S45
- Ebrahim ZY, DeBoer GE, Lueders H, Hahn JF, Lesser RP. Effect of etomidate on the electroencephalogram of patients with epilepsy 1004
- Echter E, see Coriat P
- Edmonds HL Jr, see Couture LJ
see Stolzy S
- Edström HH, see Axelsson KH
see Bridenbaugh PO
- Eger EI II, Smuckler EA, Ferrell LD, Goldsmith CH, Johnson BH. Is enflurane hepatotoxic? 21
see Carpenter RL
see Coburn CM
- Eggers GWN, see Williams WT
- Ehrenwerth J, see Smith G
- Eisele JH, see Mott JM
- Eisele JH Jr, Milstein JM, Goetzman BW. Pulmonary vascular responses to nitrous oxide in newborn lambs 62
see Kien ND
- Eisenkraft JB, Miller R, Cohen M, Toth C, Mora CT, Bernstein JL. Midazolam as an adjunct to meperidine for postoperative analgesia (abstract) S46
Pirak L, Thys DM. Monitoring neuromuscular blockade: EMG vs twitch tension (abstract) S47
see Cohen E
- El-Ganzouri ARS, see Spiess BD
- Elevi M, see Gurel A
- Ellison N, see Guffin AV
- Embree PB, see Goldhill DR
see Scott RPF
- Emery RW, see Cork RC
- Endoh H, see Kuribayashi H
- Engle JS, see Althaus JS
- Enhorning G, Pototschnik R, Possmayer F, Burgoyne R. Pulmonary surfactant films affected by solvent vapors 1275
- Epps JL, see Mesrobian RB
- Epstein BS, see Hannallah RS
- Eren A, see Gurel A
- Ergin MA, see Casthely PA
see Fyman PN
- Erickson N, see Silvay G
- Erikson JC III. Atlas of regional anesthesia (book review) 550
- Estafanous FG. Anesthesia and coronary artery surgery (book review) 993
Sethna DH, Starr NJ, Rojc K. Hemodynamic effects of neuromuscular blockers in controlled hypertensives: a randomized study (abstract) S48
see Ghattas MA
- Ethans CT, see Rice P
- Evans PJD, see Kotob HIM
- Fabian JA, Jesudian MCS, Rah KH. Double internal jugular vein cannulation in pediatric and adult cardiac surgery patients: an easy and convenient technique (letter) 419
- Fagraeus L, see Jarvis AP
see Schaefer CF
- Fahey MR, see Cannon JE
- Fahmy NR, see Cierpka H
- Faithfull NS, see Klein J
- Farag HM, Naguib M, Gyasi H, Ibrahim AW. Anesthesia for a patient with eosinophilic myositis 903
- Faraj B, see Levy JH
- Farinotti R, see Marty J
- Farrar JK, see Murkin JM
- Fauchet M, see Coriat P
- Fauss BG, Meadows JC, Bruni CY, Qureshi GD. The in vitro and in vivo effects of isoflurane and nitrous oxide on platelet aggregation 1170
- Feinberg BI, LaMantia KR, Levy WJ. Amiodarone and general anesthesia—a retrospective analysis (abstract) S49
see Konstadt SN
see LaMantia KR
- Feldman B, see Drexler H
- Feldman C, see Thorburn JR
- Feldman HS, see Rothstein P
- Feldstein GS, Waldman SD, Allen ML. Loss of resistance technique for transaortic celiac plexus block (letter) 1092
see Waldman SD
- Ferrell LD, see Eger EI II
- Feuk U, see Gordh T Jr
- Fimk BR. Mechanism of differential epidural block 325
- Finander LS, see Bloor BC
- Fine PG. Primer of water, electrolyte and acid-base syndrome (book review) 1254
- Finholt DA, Audenaert SM, Stirt JA, Marcella KL, Frierson HF Jr, Suddarth LT, Raphaely RC.

- Endotracheal tube leak pressure and tracheal lumen size in swine 667
- Stirt JA, DiFazio CA, Moscicki JC. Lidocaine pharmacokinetics in children during general anesthesia 279
see Schneider MJ
- Finlayson DC. Intensive care medicine (book review) 1255
- Finterbusch A, see Drexler H
- Fischer T, see Lynn AM
- Fisher CA, see Guffin AV
see LaMantia KR
- Fisher NA, see Lynch C III
- Fitch W, see Van Aken H
- Flacke J, see Mills C
- Flacke WE, see Bloor BC
- Flashburg MH, see Patel NJ
- Fletcher JE, see Rosenberg H
- Fletcher R, Niklason L, Drefeldt B. Gas exchange during controlled ventilation in children with normal and abnormal pulmonary circulation: a study using the single breath test for carbon dioxide 645
- Tyden H, Joachimsson P-O. Respiratory acidosis after cardiopulmonary bypass (letter) 825
- Flezzani P, Croughwell ND, McIntyre RW, Reves JG. Isoflurane decreases the cortisol response to cardiopulmonary bypass 1117
- Foëx P, see Ramsay JG
- Ford DJ, see Harrington JF
- Forrest AL. Atracurium and pheochromocytoma (letter) 211
- Fox DK, see Kim J-M
- Fox L, see Oh TH
- Fragen MP, see Avram MJ
- Frank LP. But where will I put my twitch monitor? (letter) 425
Davis RF. The effect of fentanyl on myocardial salvage in dogs after coronary artery occlusion (abstract) S50
- Freye E, Buhl RW, Ciaramelli F. Somatosensory-evoked potentials for the evaluation of analgesic properties of nalbuphine in man (abstract) S51
- Friedman R. The management of postoperative pain (book review) 996
- Frierson HF Jr, see Finholt DA
- Friesen RM, see Thomson IR
- Fromme GA, MacKenzie RA, Gould AB Jr, Lund BA, Offord KP. Controlled hypotension for orthognathic surgery 683
see Gray JR
- Frost EAM. Seizures? Drugs? Timing? (letter) 819
- Fujinaga M, Stevenson JB, Mazze RI. Reproductive and teratogenic effects of fentanyl in Sprague-Dawley rats (abstract) S52
- Fukunaga AF, see Okazaki K
- Fukunaga T, see Noda J
- Fuller J, see Gelb AW
- Furgerson CL, Sivashankaran S, Dauchot PJ. Ventilator settings to mitigate hypocarbia in the obese patient (abstract) S53
- Furman EB. International anesthesiology clinics: special problems in pediatric anesthesia (book review) 709
- Furuta T, see Cannon JE
- Furuya H, Okumura F. Hemolysis after administration of high-dose fentanyl 207
- Fusciardi J, Godet G, Bernard JM, Bertrand M, Kieffer E, Viars P. Roles of fentanyl and nitroglycerin in prevention of myocardial ischemia associated with laryngoscopy and tracheal intubation in patients undergoing operations of short duration 617
- Fyman PN, Goodman K, Casthely PA, Griep RB, Ergin MA, Smith P. Anesthetic management of patients undergoing Fontan procedure 516
see Casthely PA
- Gaines GY III, Rees DL. Electroconvulsive therapy and anesthetic considerations 1345
- Gallagher JD, see Moore RA
- Gallelli JF, see Nancherla AR
- Gallo JA, Cork RC, Kobayashi H, Puchi P. Hemodynamic effects of atracurium vs vecuronium in cardiac surgical patients (abstract) S54
see Cork RC
- Galloway FM. Analgesic potencies of dezocine and butorphanol; reply (letter) 1246
Varma S. Double-blind comparison of intravenous doses of dezocine, butorphanol, and placebo for relief of postoperative pain 283
- Galloway PA, see Glass PSA
- Gamel DM, see Barker SJ
- Gandolfi AJ, see Lind RC
see Moore RA
- Gandolfi J, see Lind RC
- Garfield FB, see Garfield JM
- Garfield JM, Garfield FB, Philip B, Earls F, Roaf E. Clinical and psychologic effects of fentanyl and nalbuphine in ambulatory surgical patients (abstract) S55
- Gasparetto A, see Rosa G
- Gauzit R, see Marty J
- Gelb AW, Fuller J, Karlik S. Anesthetics and sedatives alter tissue proton NMR relaxation properties (abstract) S56
- Gelman S. Are the requirements for hepatic injury with halothane and enflurane in rats really different? (letter) 545
- Halothane hepatotoxicity—again? (editorial) 831
- Hepatic blood flow during controlled hypotension (letter) 423
see Ebert J
see Vinik HR
- Gepts E, Heytens L, Camu F. Pharmacokinetics and placental transfer of intravenous and epidural alfentanil in parturient women 1155
- Gergis SD, see Mehta MP
- Gersonde K, see Massion WH
- Ghattas MA, Sethna DH, Rezkana H, Paganini EP, Roberts MM, Taylor PC, Loop FD, Estafanous FG. Patterns of acute renal failure (ARF) requiring dialysis after open heart surgery (abstract) S57
- Ghia JN, Levy J. Thoughts on spinal anesthesia failures from a non-teaching hospital; reply (letter) 317
- Gibbons PA, Swedlow DB. Changes in oxygen saturation during elective tracheal intubation in infants (abstract) S58
see Adler E
- Gielen MJM, see Bridenbaugh PO
- Giesecke AH, see Walmsley AJ
- Giesecke AH Jr, see Murphy MT
- Gillman MA, Lichtigfeld FJ. Naloxone-morphine synergism: support for dual system hypothesis of pain perception (letter) 313
- Gillmor ST, see Streisand JB
- Gingerich S, see Lippmann M
- Gladines MPRR, see Burn AGL
- Glass PSA, Galloway PA. Prolonged QT interval syndromes; reply (letter) 213
- Glazener CH, see Motoyama EK
- Glenn JJ, see Moffitt EA
- Globerson JH, see Wilton NCT
- Godet G, see Fusciardi J
- Goetzl EJ, see Swerdlow BN
- Goetzman BW, see Eisele JH Jr
- Gold MI, see Abraham EC
- Goldberg ME, see Azad SS
- Goldhill DR, Embree PB, Ali HH, Savarese JJ. Complete reversal of deep pancuronium block requires at least 20 minutes (abstract) S59
- Martyn JAJ, Kim EM, Hoaglin DC. Effect in dogs of selective beta blockade on potassium release after succinylcholine (abstract) S60
- Goldman ME, see Hillel Z
see Thys DM
- Goldsmith CH, see Eger EI II
- Goode JG, Wetmore RF, Keon TP.

- Anesthetic management of child with an intratracheal tumor 1227
 Goodman K, see Casthely PA
 see Fyman PN
- Gordh T Jr, Feuk U, Norlén K. Effect of epidural clonidine on spinal cord blood flow and regional and central hemodynamics in pigs 1312
- Post C, Olsson Y. Evaluation of the toxicity of subarachnoid clonidine, guanfacine, and a substance P-antagonist on rat spinal cord and nerve roots. Light and electron microscopic observations after chronic intrathecal administration 1303
- Goresky GV, see Sale JP
- Goroszeniuk T, Albin M, Jones RM. Generalized grand mal seizure after recovery from uncomplicated fentanyl-etomidate anesthesia 979
- Goudsouzian NG, Standaert FG. The infant and the myoneural junction 1208
- Young ET, Moss J, Liu LMP. Histamine release during the administration of atracurium and vecuronium in children (abstract) S61
 see deBros FM
 see Hagen J
 see Young ET
- Gould AB Jr, see Fromme GA
- Graham DI, see Van Aken H
- Graham TM, Chang KSK, Stevens WC. Arterial oxygen desaturation and effect of supplemental O₂ during transit from or to PAR utilizing a pulse oximeter (abstract) S62
- Grant G, Ramanathan S, Patel N, Dursztman M, Arismendy J, Turndorf H. The effects of local anesthetics on maternal and neonatal platelet function (abstract) S63
- Gray JR, Fromme GA, Nauss LA, Wang JK, Ilstrup DM. Intrathecal morphine for post-thoracotomy pain 873
 see Ramanathan S
- Greeley WJ. Cardiac catheterization and angiography (book review) 1094
- Greenblatt DJ, Locniskar A, Scavone JM, Blyden GT, Ochs HR, Harmatz JS, Shader RI. Absence of interaction of cimetidine and ranitidine with intravenous and oral midazolam 176
- Greene ER. Intravascular injection of local anesthetic after venipuncture of axillary vein during attempted brachial plexus block (letter) 421
- Spinal and epidural anesthesia in patients with acquired immunodeficiency syndrome (letter) 1090
- Greene ER Jr. Acquired immunodeficiency syndrome: an overview for anesthesiologists 1054
- Greene SJ, Cane RD, Shapiro BA. A foam cuff endotracheal tube T-piece system for use with nitrous oxide anesthesia 1359
- Greene WB, see Kafer ER
- Greenwalt JW, see Jarvis AP
- Gregoretti S, Vinik HR. Sufentanil pharmacokinetics in burn patients undergoing skin-grafting (abstract) S64
- Griep RB, see Casthely PA
 see Fyman PN
- Griffin RM, Kaplan JA. Comparison of ECG leads V5, CS5, CB5, and II by computerized ST segment analysis (abstract) S65
- Grogono AW. Current European anaesthesiology (volume 1) (book review) 995
- Gronert GA. Molecular and cellular mechanisms of anesthetics (book review) 1371
- Resistance to pancuronium (letter) 539
 see Lennon RL
- Grosslight KR, Rowlingson JC, Boaden RW. Herpes zoster and reflex sympathetic dystrophy 309
 see DiFazio CA
- Grossman R, see Patel NJ
- Grynstejn M, see Thiagarajah S
- Guffin AV, Kaplan JA, Fisher CA, Ellison N, Addonizio VP. The effect of slow channel calcium blockers on preoperative platelet function (abstract) S66
 see Zaidan JR
- Gugino LD, see Mark JB
- Guiraudon G, see Murkin JM
- Gürel A, Ünal N, Elevi M, Eren A. Epidural morphine for postoperative pain relief in anorectal surgery 499
- Gyasi H, see Farag HM
 see Naguib M
- Haberer J-P, see Dalens B
- Hagen J, Martyn J, Szyfelbein SK, Goudsouzian NG. Cardiovascular and neuromuscular responses to high-dose pancuronium-metocurine in pediatric burned and reconstructive patients 1340
- Hagen TJ, see Hoffman WE
- Hagenouw RRP, Bridenbaugh PO, Van Egmond J, Steubing R. Tourniquet pain: a volunteer study 1175
 see Bridenbaugh PO
- Hägmark S, see Nath S
- Hague B, see Mock DL
- Hahn JF, see Ebrahim ZY
- Halaburt AS, see Pagden D
- Halliday NJ, see Dundee JW
- Halpern NB, see Vinik HR
- Hamar O, Csömör S Jr, Kazy Z, Vigváry Z. Epidural morphine analgesia by means of a subcutaneously tunneled catheter in patients with gynecologic cancer 531
- Hamilton WK. Matters of life and death: risks vs benefits of medical care (book review) 1096
- Measures of outcome (letter) 422
- Hand CW, see Jamous MA
 see Kotob HIM
- Hannallah RS, Oh TH, McGill WA, Epstein BS. Changes in heart rate and rhythm after intramuscular succinylcholine with or without atropine in anesthetized children 1329
- Hansen DD, Hickey PR. Anesthesia for hypoplastic left heart syndrome: use of high-dose fentanyl in 30 neonates 127
- Hickey PR. Hemodynamic effects of N₂O in infants (abstract) S67
- Hansen T, see Kafer ER
- Hantler CB, Wakefield TW, Knight PR, Whitehouse WM, Ketcham TR, Tuttle DB, Stanley JC. Self taming doses of protamine prevent subsequent protamine hypotension (abstract) S68
- Harley D, see Lippmann M
- Harmatz JS, see Greenblatt DJ
- Harper KW, see Dundee JW
- Harrington JF, Ford DJ. Myoglobinemia after succinylcholine in children undergoing isoflurane anesthesia (abstract) S69
- Harris C, see Ebert J
 see Vinik R
- Harris MM. 1985 Yearbook of anesthesia (book review) 709
- Harrison DM, see Hyde NH
- Harrison JL. Postoperative seizures after isoflurane anesthesia 1235
- Harrison WK, see Sanford TJ Jr
- Harte E, see Baysinger CL
- Hartley C, see Hysing ES
- Hartwell BL, Mark JB. Combinations of beta-blockers and calcium channel blockers: a cause of malignant perioperative conduction disturbances? 905
 see Mark JB
- Hatano Y, see Arai T
- Hatch D, see Breen PH
- Hatem J, see Baraka A
- Heal A, see Szeinfeld M
- Healy TEJ, see Bolder PM
- Heavner JE. Cardiac dysrhythmias induced by infusion of local

- anesthetics into the lateral cerebral ventricle of cats 133
see Racz GB
- Hegab E-S, Matulionis DH. Pulmonary macrophage mobilization in cigarette smoke-exposed mice after halothane anesthesia 37
- Hegland MG, see Koehntop DE
- Heifetz M, see Levin H
- Heller J, see Shah K
- Henling CE, Reves JG, Samuelson PN, Lell WA, Bradley EL, Kirklin JK, McGiffin DC, Zorn GL, Kreusch GR, Adams ML. Hemodynamic effects of continuous infusion of esmolol during cardiac operation (abstract) S70
- Henning RJ, Heyman V, Alcover I, Romeo S. Cardiopulmonary effects of oleic acid-induced pulmonary edema and mechanical ventilation 925
- Hensley FA Jr, see Skeehan TM
- Henzel C, see Marty J
- Herrington CA, see Abraham EC
- Hessel EA II, see Owens EL
- Heyman V, see Henning RJ
- Heytens L, see Gepts E
- Hickey PR, see Hansen DD
- Higashi H, see Kuribayashi H
- Hilavacek JR, Restifo R, Stone D, Cullen D. Laboratory false-positive hyperkalemia in a patient with cold agglutinins (letter) 1247
- Hilgenberg A, see Mastrocostopoulos G
- Hilkenes P, see Streisand JB
- Hill CR, see Schultetus RR
- Hill RF, see Kates RA
- Hillel Z, Thys D, Goldman ME, Mindich BP, Kahan F, Kaplan JA. Halothane produces dose-dependent myocardial depression in man during fentanyl anesthesia (abstract) S71
- Thys D, Mindich BP, Goldman ME, Kaplan JA. A new method for the intraoperative determination of contractility (abstract) S72
see Thys DM
- Hines R, Barash PG. Protamine: does it alter right ventricular function? 1271
see Biondi J
see Smith G
- Hinohara T, see Kates RA
- Hirsch IA, Zauder HL. Chloral hydrate: a potential cause of arrhythmias 691
- Hirsch N, Smith GB. Cushing's contributions to anesthesia: two comments; reply (letter) 1251
see Smith G
- Hirshman CA, see North C
- Hjortso N-C, Lund C, Mogensen T, Bigler D, Kehlet H. Epidural morphine improves pain relief and maintains sensory analgesia during continuous epidural bupivacaine after abdominal surgery 1033
- Hlatky MA, see Kates RA
- Hoaglin DC, see Goldhill DR
- Hoffman B, see Perel A
- Hoffman WE, Albrecht RF, Miletich DJ, Hagen TJ, Cook JM. Cerebrovascular and cerebral metabolic effects of physostigmine, midazolam, and a benzodiazepine antagonist 639
- Miletich DJ, Albrecht RF. The effects of midazolam on cerebral blood flow and oxygen consumption and its interaction with nitrous oxide 729
- Hoiland-Carlsen PF, see Chraemmer-Jorgensen B
- Holaday JW, see Schaefer CF
- Hollier LH, see Blaise GA
- Hornbein TF, see Townes BD
- Houwertjes MC, see Schwarz S
- Howard C, see Nancherla AR
- Howe JG, see Perkins FM,
see Stern P
- Howell ML, see Rees DI
- Howie MB, Mortimer W, McSweeney TD, Silver MJ. Muscle relaxant—beta blocker interactions during high dose narcotic induction (abstract) S73
- Howland WS, see Rooney SM
- Hoyt JW. Case studies in critical care medicine (book review) 323
Update in intensive care and emergency medicine (book review) 322
- Hudson RJ. Variability of fentanyl pharmacokinetics in neonates (letter) 1369
- Hufstедler S, see Barker SJ
- Hug CC Jr, see Newsome LR
- Hui GS, see Artru AA
- Hunter LW, Rorie DK, Tyce GM. Norepinephrine uptake in canine saphenous veins in the presence and absence of halothane 360
- Hurley RJ, see Datta S
- Hutchinson BR, Merry AF. Acid aspiration risk factors (letter) 210
- Hwang TF, see Bosnjak ZJ
- Hyatt J, see Barker SJ
- Hyde NH, Harrison DM. Intrathecal morphine in a parturient with cystic fibrosis 1357
- Hyman SA, see Kambam JR
- Hynynen MJ, Turunen MT, Korttila KT. Effects of alfentanil and fentanyl on common bile duct pressure 370
- Hysing ES, Chelly J, Doursout M-F, Merin RG, Hartley C. Isoflurane changes the cardiac and regional effects of the calcium channel blocker nicardipine in dogs (abstract) S74
- Ibrahim AW, see Farag HM
- Ilstrup DM, see Gray JR
- Imrie DD, Moffitt EA, McIntyre AJ, Cousins CL, Kinley CE, Sullivan JA, Murphy DA. Myocardial metabolism and hemodynamics in hypertensive coronary patients given fentanyl-enflurane, anesthesia (abstract) S75
see Moffitt EA
- Ingram M, see Cook DR
- Isern M, see Bailey PL
- Ishida H, see Arai T
- Ishizawa Y, Yamaguchi H, Dohi S, Koyama K. A serious complication due to gastrointestinal malfunction in a patient with myotonic dystrophy 1066
- Islas J-A. Epidural ketamine for control of postoperative pain: two comments; reply (letter) 990
- Isley AH, see Mather LE
- Isley MR, see Kafer ER
- Ivankovich AD, McCarthy RJ, Brock-Utne JG, Rubin J, Mankowitz E. Epidural ketamine for control of postoperative pain: two comments (letter) 989
see Badrinath S
see Braverman B
see Spiess BD
- Jabons M, see Casthely PA
- Jakymec AJ, see Navalgund AA
- James MFM, Cork RC, Dennett JE. Succinylcholine pretreatment with magnesium sulfate 373
see Nicoll JMV
see Thorburn JR
- James PD, Volgyesi GA, Burrows FA. Alpha-pattern EEG during pediatric cardiac operations under isoflurane anesthesia 525
- Jamous MA, Hand CW, Moore RA, Teddy PJ, McQuay HJ. Epinephrine reduces systemic absorption of extradural diacetylmorphine 1290
- Janesheski JA, see Townes BD
- Jaoude CA, see Baraka A
- Jaraki K, see Baraka A
- Jarvis AP, Greenwalt JW, Fagraeus L. Intravenous caffeine for postdural puncture headache (letter) 315
- Jeavons P, see Ramsay JG
- Jebeles JA, Kissin I, Bradley EL Jr. Spinal and supraspinal mechanisms for morphine-pentobarbital antinociceptive interaction in relation to cardiac acceleration response in rats 601
- Jebson PJ, see Pearson KS
- Jensen BN, see Petring OU
- Jesudian MCS, see Fabian JA

- Jeter JN, see Ramanathan J
 Joachimsson P-O, see Fletcher R
 Jobes DR, see Nicolson SC
 Johansson G, see Nath S
 Johns RA, see DiFazio CA
 Johnson BH, see Carpenter RL
 see Eger EI II
 Johnson JC, see Prough DS
 Johnson S, see Zaidan JR
 Jones LA, see Ramsay JG
 Jones MM, see Younker D
 Jones P, see Britt BA
 Jones RM, see Goroszeniuk T
 Joyce TH III, see Younker D
 Judson P, see Shanks CA
 Kafer ER, Isley MR, Hansen T, Lineberger A, Miller DT, Owen H, Schur MS, Greene WB. Automated acute normovolemic hemodilution reduces blood transfusion requirements for spinal fusion (abstract) S76
 Kahan F, see Hillel Z
 Kaine CJ, see Kuhnert BR
 Kalkman CJ, see Van Rheineck Leyssius AT
 Kalli I, see Meretoja OA
 Kambam JR, Chen LH, Hyman SA. Effect of short-term smoking halt on carboxyhemoglobin levels and P₅₀ values 1186
 Kampine JP, see Bosnjak ZJ
 Kaplan JA, see Cohen E
 see Griffin RM
 see Guffin AV
 see Hillel Z
 see Silvey G
 see Thys DM
 see Twerskey RS
 see Wojtczak JA
 Kappa J, see LaMantia KR
 Kapur PA, Campos JH, Buchea OC. Plasma diltiazem levels, cardiovascular function, and coronary hemodynamics during enflurane anesthesia in the dog 918
 Campos JH, Tippit SE. Influence of diltiazem on cardiovascular function and coronary hemodynamics during isoflurane anesthesia in the dog: correlation with plasma diltiazem levels 81
 see Campos JH
 see Makela VHM
 see Sullivan KB
 Karam H, see Baraka A
 Kareti RKP. Comparison of perioperative factors affecting potassium requirements between CABG vs valve patients during postoperative period (abstract) S77
 Postassium requirements following coronary artery bypass graft (CABG) surgery: the effect of perioperative factors (abstract) S78
 Karlik S, see Gelb AW
 Karlman R, see Shah K
 Karyn A, see Pagden D
 Kasten GW, Martin ST. Comparison of resuscitation of sheep and dogs after bupivacaine-induced cardiovascular collapse 1029
 Martin ST. Resuscitation from bupivacaine-induced cardiovascular toxicity during partial inferior vena cava occlusion 341
 Owens E. Evaluation of lidocaine as an adjunct to fentanyl anesthesia for coronary artery bypass graft surgery 511
 see Owens EL
 Kataria BK, Lampkins R. Nail polish does not affect pulse oximeter saturation (letter) 824
 Kates RA, Stack RS, Hill RE, Carlson EB, Hinohara T, Hlatky MA, Reves JG. General anesthesia for patients undergoing percutaneous transluminal coronary angioplasty during acute myocardial infarction 815
 Katz NM, see Walter RR
 Kaufman RD, see Khoury GF
 Kay B. Prolonged myoclonus after etomidate anesthesia (letter) 992
 see Bolder PM
 Kazy Z, see Hamar O
 Keegan CR, see Silbert BS
 Kehlet H, see Hjortso N-C
 Kempen PM. Anesthesia (book review) 994
 Static and dynamic considerations in gastric barotrauma (letter) 540
 Keon TP, see Goode JG
 Kerns D, see Moore RA
 Kerr CR, see Chung DC
 Kersten UW, see Bencini AF
 see Meistelman C
 see Sohn YJ
 Ketcham TR, see Hantler CB
 Khalil M, see Ramanathan J
 Khoury GF, Kaufman RD, Musich JA, Mogard M. Neurotensin and vasoactive intestinal peptide levels during orthotopic liver transplantation (abstract) S79
 Kieffer E, see Fusciardi J
 Kien ND, Reitan JA, White DA, Wu C-H, Eisele JH Jr. Hemodynamic responses to alfentanil in halothane-anesthetized dogs 765
 Kim EM, see Goldhill DR
 Kim J-M, Arakawa K, Benson KT, Fox DK. Pulse oximetry and circulatory kinetics associated with pulse volume amplitude measured by photoelectric plethysmography 1333
 Kim KC, Tasch MD. Effects of cimetidine and ranitidine on local anesthetic central nervous system toxicity in mice 840
 Kim YD, see Nancherla AR
 see Shin YK
 see Walter RR
 Kimovec MA, Serpico LC, Sloan TB, Kol A, Calvin AO. Effects of thiopental on cerebral evoked potentials (abstract) S80
 see Koht A
 Kingsley CP, Schmidt SI, Reynolds WJ. . . method for securing "piggyback" infusions (letter) 209
 Kingston HGG. Halothane and isoflurane anesthesia in pediatric outpatients 181
 Induction of anesthesia with isoflurane in children; reply (letter) 366
 Kinley CE, see Imrie DD
 see Moffitt EA
 Kinzer J, see Shanks CA
 Kirby RR. Acute respiratory failure (book review) 214
 Kirklin JK, see Henling CE
 see Samuelson PN
 Kirschenbaum LP, see Rowlingson JC
 Kirschner PA, see Cohen E
 Kissin I, Mason JO III, Bradley EL Jr. Morphine and fentanyl interaction with thiopental in relation to movement response to noxious stimulation 1149
 Morphine-halothane interaction controversy (letter) 319
 see Castillo R
 see Jebeles JA
 Kitahata LM, see Matsumoto M
 Klaunig JE, see Nigrovic V
 Kleiman A, see Britt BA
 Klein J, Faithfull NS, Salt PJ, Trouwborst A. Transperitoneal oxygenation with fluorocarbons 734
 Klein SL. Anesthesia and sedation in the dental office (book review) 1094
 Kleinman B, Belusko R. Delayed cephalic spread of a lidocaine spinal anesthetic causing ventilatory failure 523
 Knight PR, see Hantler CB
 Kobayashi H, see Gallo JA
 Koehntop DE, Rodman JH, Brundage DM, Hegland MG, Buckley JJ. Pharmacokinetics of fentanyl in neonates 227
 see Rodman J
 Koht A, Kimovec MA, Sloan TB, Calvin AO. The effects of sufentanil on median nerve somatosensory evoked potentials (abstract) S81
 see Kimovec MA
 see Sloan TB
 Komatsu T, Shibutani K, Okamoto K,

- Kumar V, Kubal K, Sanchala V. Comparison of sufentanil-diazepam and fentanyl-diazepam anesthesia for induction (abstract) S82
see Shibutani K
- Kondo Y, see Matsumiya N
- Kong D, see Konstadt SN
see Prough DS
- Konowitz H, see Vender JS
- Konstadt SN, Feinberg B, Thys DM, Kong D, Mindich BP, Watkins WD. Prostacyclin and thromboxane changes associated with protamine administration (abstract) S83
- Kopf G, see Oh TH
see Rothstein P
- Koren G, see Sale JP
- Korttila KT, see Hynynen MJ
- Kotob HIM, Hand CW, Moore RA, Evans PJD, Wells J, Rubin AP, McQuay HJ. Intrathecal morphine and heroin in humans: six-hour drug levels in spinal fluid and plasma 718
- Koyama K, see Ishizawa Y
- Kozody R, see Bedder MD
see Ong BY
- Kreusch GR, see Henling CE
- Kron IL, see Lake CL
- Kubal K, see Komatsu T
- Kuhnert BR, Kuhnert PM, Philipson EH, Syracuse CD, Kaine CJ, Chang-hyon Y. The half-life of 2-chloroprocaine 273
Philipson EH, Pimental R, Kuhnert PM, Zuspan KJ, Syracuse CD. Lidocaine disposition in mother, fetus, and neonate after spinal anesthesia 139
- Kuhnert PM, see Kuhnert BR
- Kumar V, see Komatsu T
see Mehta MP
- Kunjappan VE, Brown EM, Alexander GD. Rapid sequence induction using vecuronium 503
- Kuribayashi H, Endoh H, Sato K, Sato Y, Higashi H, Shimoji K. Naloxone attenuates hypoxic depression of ganglionic transmission 489
- Kutt JL, see Lam AM
- LaMantia KR, Feinberg BI, Fisher CA, Kappa J, Addonizio VP. Protamine, white cells, platelets and eicosanoids: does pulmonary hypertension make a difference? (abstract) S86
see Feinberg BI
- Lai A, see deBros FM
- Lake CL. Morphine-halothane interaction controversy; reply (letter) 320
Perioperative cardiac dysrhythmias: mechanisms, recognition, management (book review) 106
Kron IL, Mentzer RM, Crampton RS. Lidocaine enhances intraoperative ventricular defibrillation 337
- Lam AM, Brown SC, Manninen PH. Pharmacokinetic study of isoflurane in man—uptake into brain (abstract) S84
Manninen PH, Contreras J, Diamond C, Kutt JL, Penny F. Monitoring of somatosensory evoked responses during cardiopulmonary bypass—the influence of temperature (abstract) S85
see Newman B
- Lambert DH, see Datta S
see Urmev WF
- Lampert BA. Vaporizer output increases when nitrous oxide is eliminated as a carrier gas (letter) 823
- Lampkins R, see Kataria BK
- Landymore RW, see Moffitt EA
- Lappas DG, see Mastrocostopoulos G
- Larijani GE, see Sosis M
- Larsen RH, see Liao JC
- Latta WB, see Silbert BS
- Leahy JJ. The origins of anaesthesia (book review), 323
- Lear E, see Thiagarajah S
- Lee C, Peachman FA. Unilateral hearing loss after spinal anesthesia treated with epidural blood patch 312
see Mok MS
see Tsai SK
- Lee TS, see Lippmann M
- Lee TY, see Mok MS
see Tsai SK
- Lees DE, see Shibutani K
- Lefevre P, see Marty J
- Leicht CH, Carlson SA. Prolongation of lidocaine spinal anesthesia with epinephrine and phenylephrine 365
- Lell WA, see Henling CE
- Lennon RL, Olson RA, Gronert GA. Vecuronium or atracurium for rapid sequence intubation (abstract) S87
- Lerner MP, see Schaefer CF
- Lesser RP, see Ebrahim ZY
- Letourneau J, see Denis R
- Levin ED, Bowman RE. Behavioral effects of chronic exposure to low concentrations of halothane during development in rats 653
- Levin H, Bursztein S, Heifetz M. Prestenotic dilation of the esophagus: a hazard of internal jugular vein cannulation 901
- Levin LL, Winter PM, Nemoto EM, Uram M, Lin MR. Naloxone does not antagonize the analgesic effects of inhalation anesthetics 330
- Levron JC, see Chauvin M
- Levy J, Zaidan JR, Faraj B. Prospective evaluation of risk of protamine reactions in patients with NPH insulin-dependent diabetes 739
see Ghia JN
- Levy WJ, see Feinberg BI
- Liao JC, Belani KG, Mikhail S, Rinker RM, Larsen RH, Lund GP, Buckley JJ. Use of new anesthesia circuit for remote ventilation during magnetic resonance imaging (abstract) S88
- Lichtenthal PR, see Wong HY
- Lichtigfeld FJ, see Gillman MA
- Lienhart A, see Bencini AF
- Lin MR, see Levin LL
- Lind RC, Gandolfi AJ, Sipes IG, Brown BR Jr, Waters SJ. Oxygen concentrations required for reductive defluorination of halothane by rat hepatic microsomes 835
Gandolfi J, Brown BR Jr. Are the requirements for hepatic injury with halothane and enflurane in rats really different?; reply (letter) 545
- Lineberger A, see Kafer ER
- Lippman M. Analgesic potencies of dezocine and butophanol (letter) 1246
Paicius R, Gingerich S, Owens R, Mok MS, Charney J, Lee TS, Harley D, Verespej J, Appel P. A controlled study of the hemodynamic effects of propofol vs thiopental during anesthesia induction (abstract) S89
- Lipton JM, see Murphy MT
see Walmsley AJ
- Liu LMP, see Goudsouzian NG
- Lockhart CH, see Morrison JE Jr
- Locniskar A, see Greenblatt DJ
- Logan MR, see Drummond GB
- Lomholt N, see Petring OU
- Londorf D, see Denis R
- Long D, see Toung TJK
- Loomis CW, see Nakatsu K
- Loop FD, see Ghattas MA
- Loose J-P, see Meistelman C
- Loubser PG. Complement activation during surgery with and without cardiopulmonary bypass (abstract) S90
- Lovitz M, see Puig M
- Lowry RL, see Williams WT
- Lu CC, see Tsai SK
- Lubenow TR, see Spiess BD
- Luders H, see Ebrahim ZY
- Luerssen TG, see Schubert A
- Lunam CA, Cousins MJ, de la M. Hall P. Genetic predisposition to liver damage after halothane anesthesia in guinea pigs 1143
- Lund BA, see Fromme GA
- Lund C, see Hjortso N-C
- Lund GP, see Liao JC
- Lurie CR, see Szeinfeld M

- Lynch C III. Depression of myocardial contractility in vitro by bupivacaine, etidocaine, and lidocaine 551
- Durbin CG Jr, Fisher NA, Veselis RA, Althaus JS. Effects of dantrolene and verapamil on atrioventricular conduction and cardiovascular performance in dogs 252
- Lynn AM, Fischer T, Brandford HG, Pendergrass TW. Systemic responses to tourniquet release in children 865
- MacIntyre CJ, see Ong BY
- MacKenzie RA, see Fromme GA
- Macciolo GA, see Sprague DH
- Machado R, see Szeinfeld M
- Macnamara TE, see Nancherla AR
see Walter RR
- Maddi R, see Mark JB
- Maguire D, see Azad SS
- Makela VHM, Kapur PA. Dose related cardiovascular effects of amrinone during enflurane anesthesia in the dog 849; (abstract) S91
- Maltby JR, Sutherland AD, Sale JP, Shaffer EA. Preoperative oral fluids: is a five-hour fast justified prior to elective surgery? 1112
- Manchikanti L, Roush JR, Colliver JA. Effect of preanesthetic ranitidine and metoclopramide on gastric contents in morbidly obese patients 195
see Colliver JA
- Maness R, see Vinik R
- Mankowitz E, see Ivankovich AD
- Manninen PH, see Lam AM
- Mansour R, see Baraka A
- Marcella KL, see Finholt DA
- Mark JB, Steinbrook RA, Gugino LD, Maddi R, Hartwell B, Shemin R, DiSesa V, Rida WN. Continuous noninvasive monitoring of cardiac output with esophageal Doppler ultrasound during cardiac surgery 1013
see Hartwell BL
see Wakerlin G
- Maroko PR, see Davis RF
- Marr AT, see Sosis M
- Marsh B, see North C
see Wetzel RC
- Marshall BE. Handbook of physiology, section 3: the respiratory system. Volume 1. Circulation and nonrespiratory functions (book review) 426
- Marshall JR. Guidelines in clinical anaesthesia (book review) 996
- Martin DC, see Townes BD
- Martin JT, see Pandya JB
- Martin R, Petit B, Basora J. A regional anesthetic technique compared to general anesthesia for outpatient knee arthroscopy (letter) 1091
- Martin ST, see Kasten GW
- Marty J, Gauzit R, Lefevre P, Couderc E, Farinotti R, Henzel C, Desmonts JM. Effects of diazepam and midazolam on baroreflex control of heart rate and on sympathetic activity in humans 113
- Martyn J, see Goldhill DR
see Hagen J
- Marving J, see Chræmmer-Jørgensen B
- Mason JO III, see Kissin I
- Massion WH, Schubert K, Gersonde K. Oxygen-hemoglobin affinity changes during open heart surgery (abstract) S92
- Mastrocostopoulos G, Athanasiadis C, Skourtis C, Palacios I, Hilgenberg A, Lappas DG. Regional and global myocardial metabolic and coronary hemodynamic effects of halothane in cardiac patients during high dose sufentanil anesthesia (abstract) S93
- Matayoshi Y, see Sari A
- Mather LE, Runciman WB, Carapetis RJ, Isley AH, Upton RN. Hepatic and renal clearances of lidocaine in conscious and anesthetized sheep 943
- Matjasko J. Controlled hypotension in neuroanesthesia (book review) 322
- Matsumiya N, Dohi S, Takahashi H, Kondo Y, Naito H. Cardiovascular collapse in an infant after caudal anesthesia with a lidocaine-epinephrine solution 1074
- Matsumoto M, Collins JG, Kitahata LM, Yuge O, Tanaka A. A comparison of the effects of alfentanil applied to the spinal cord and intravenous alfentanil on noxiously evoked activity of dorsal horn neurons in the cat spinal cord 145
- Matteo RS, Ornstein E, Young WL, Schwartz AE, Port M, Chang WJ. Pharmacokinetics of sufentanil in the elderly (abstract) S94
see Ornstein E
see Silverberg PA
- Matthay MA, see Swerdlow BN
- Matthay RA, see Biondi JW
- Matthew EB, see Vender JS
- Matulionis DH, see Hegab E-S
- Matz SD, see Spiess BD
- Mayhew JF. Hypertensive response to Dinoprost under anesthesia (letter) 1248
- Mazzi RI, see Fujinaga M
- McArthur JD, see Williams JP
- McCarthy RJ, see Ivankovich AD
- McCollum JSC, see Dundee JW
- McDonald JS, see Stock MC
- McGarrigle RE, Stuart S, Baumgartner WA, Blanck TJJ. Reinfarction following anesthesia and CABG for post-infarction unstable angina (abstract) S95
- McGiffin DC, see Henling CE
- McGill WA, see Hannallah RS
- McIntyre AJ, see Imrie DD
see Moffitt EA
- McIntyre RW, see Flezzani P
- McMichan JC, see Blaise GA
see Murray MJ
- McNicholas KW, see Moore RA
- McPherson RW. Spinal injury (book review) 996
see Toung TJK
- McQuay HJ, see Jamous MA
see Kotob HIM
- McShane AJ, see Wren WS
- McSweeney TD, see Howie MB
- McVey JR, see Williams L
- Meadows JC, see Fauss BG
- Meeuwis H, see Van Zundert A
- Mehta MP, Choi WW, Kumar V, Gergis SD, Sokoll MD. Safety and efficacy of OH 101—mixture of edrophonium and atropine. A reversal agent (abstract) S96
- Gergis SD, Sokoll MD. Accelerated onset of pancuronium, atracurium, and vecuronium. A comparison to succinylcholine (abstract) S97
- Meistelman C, Agoston S, Kersten UW, Saint-Maurice C, Bencini AF, Loose J-P. Pharmacokinetics and pharmacodynamics of vecuronium and pancuronium in anesthetized children 1319
see Bencini AF
- Menk EJ, see Baysinger CL
- Mentzer RM, see Lake CL
- Meretoja OA, Kalli I. Spontaneous recovery of neuromuscular function after atracurium in pediatric patients 1042
- Merin RG, see Hysing ES
- Merry AF, see Hutchinson BR
- Mesrobian RB, Epps JL. Midtracheal obstruction after Harrington rod placement in a patient with Marfan's syndrome 411
- Meyer RM. Esophageal stethoscopes can reveal light anesthesia (letter) 319
- Michenfelder JD, see Milde LN
- Middaugh R, see Baysinger CL
- Mihm FG, see Cheng EY
see Swerdlow BN
- Mikhail S, see Liao JC
- Milde JH, see Milde LN
- Milde LN, Milde JH, Michenfelder JD. Delayed nimodipine treatment improves cerebral blood flow after

- complete cerebral ischemia in dogs (abstract) S98
- Miletich DJ, see Becker GL
- see Hoffman WE
- Millar K. Psychomotor tasks and recovery from anesthesia (letter) 543
- Miller DT, see Kafer ER
- Miller ED Jr, see Althaus JS
- Miller J, see Cope DK
- see Mills C
- Miller R, see Cannon JE
- see Eisenkraft JB
- Mills C, Flacke J, Miller J, Davis J. The cardiovascular effects of fentanyl reversal by naloxone at varying arterial CO₂ tensions in dogs (abstract) S99
- Milstein JM, see Eisele JH Jr
- Mindich BP, see Hillel Z
- see Konstadt SN
- see Silvey G
- see Thys DM
- Minton MD, Stirt JA, Bedford RF. Effect of succinylcholine on serum potassium in patients with brain tumors (abstract) S100
- Stirt JA, Bedford RF. Vecuronium and intracranial pressure in man (abstract) S101
- Miyauchi Y, see Sari A
- Mizoi Y, see Noda J
- Mock DL, Streisand JB, Hague B, Dzelzkalns RR, Bailey PL, Pace NL, Stanley TH. Transmucosal narcotic delivery: an evaluation of fentanyl (lollipop) premedication in man (abstract) S102
- Moffitt EA, Barker RA, Glenn JJ, Imrie DD, DelCampo C, Landymore RW, Kinley CE, Murphy DA. Myocardial metabolism and hemodynamic responses with isoflurane anesthesia for coronary arterial surgery 53
- McIntyre AJ, Barker RA, Imrie DD, Murphy DA, Landymore RW, Kinley CE. Myocardial metabolism and hemodynamic responses with fentanyl-enflurane anesthesia for coronary arterial surgery 46
- Sethna DH. The coronary circulation and myocardial oxygenation in coronary artery disease: effects of anesthesia 395
- see Imrie DD
- Mogard M, see Khoury GF
- Mogensen T, see Hjortso N-C
- Mok MS, Tsai SK, Lee TY, Chen WS, Wang JJ, Lee C. Facilitation of endotracheal intubation with a priming dose of atracurium in children (abstract) S103
- see Lippmann M
- see Tsai SK
- Moleski R, Barash PG. Controlled drug accountability; reply (letter) 540
- Monroe S, see Zaidan JR
- Montebault C, see Chauvin M
- Moore J, Dundee JW. A comparison of the maternal stress response during cesarean delivery with general or epidural anesthesia (abstract) S104
- see Wilson CM
- Moore RA, McNicholas KW, Gallagher JD, Gandolfi AJ, Sipes IG, Kerns D, Ckark DL. Halothane metabolism in acyanotic and cyanotic patients undergoing open heart surgery 1257
- see Jamous MA
- see Kotob HIM
- Mora CT, see Eisenkraft JB
- Mori K, see Arai T
- see Noda J
- Morrison JE Jr, Lockhart CH. Tourette syndrome: anesthetic implications 200
- Morrison P, see Breen PH
- Morrow DH. *Precis d'anesthésie loco-regionale* (book review) 107
- Mortimer W, see Howie MB
- Moscicki JC, see Althaus JS
- see DiFazio CA
- see Finholt DA
- Moss J, see Goudsouzian NG
- see Silbert BS
- Moss P, see Vaida GT
- Motoyama EK, Glazener CH. Hypoxemia after general anesthesia in children 267
- Mott JM, Eisele JH. A survey of monitoring practices following spinal opiate administration (abstract) S105
- Moyer GA, Rein P. Preoxygenation in the morbidly obese patient (abstract) S106
- Moyers JR. Advances in anesthesia (book review) 994
- Moyes DG, see Thorburn JR
- Muallem M, see Baraka A
- Mundler O, see Coriat P
- Munson ES, see Pittinger CB
- Murakawa K, Abboud TK, Yanagi T. Neonatal responses to alphaprodine administered during labor 392
- Murata KN, see Cremonesi E
- Muravchick S. Anaesthesia in the elderly (book review) 993
- see Weber S
- Murkin JM, Farrar JK, Tweed WA, Guiraudon G. Cerebral blood flow, oxygen consumption and EEG during isoflurane anesthesia (abstract) S107
- Murphy AL, see Silbert BS
- Murphy DA, see Imrie DD
- see Moffitt EA
- Murphy MT, Lipton JM, Giesecke AH Jr. Postanesthetic shivering: incidence and implications in the elderly patient (abstract) S108
- Murray MJ, McMichan JC, Wignes M. Assessment of sterility of pulmonary arterial catheter sheaths (abstract) S109
- Wignes M, McMichan JC. Assessment of sterility of pulmonary arterial catheter sheaths 1218
- Murthy VS, see Bosnjak ZJ
- Musich JA, see Khoury GF
- Myers JA, see Denson DD
- Nadeau SG, Robblee JA. Effect of premedication on arterial blood gases in cardiac surgical patients (abstract) S110
- Nagle D, see Newsome LR
- Naguib M, Abdulatif M, Gyasi HK, Absood GH. Priming with atracurium: improving intubating conditions with additional doses of thiopental 1295
- see Farag HM
- Naito H, see Dohi S
- see Matsumiya N
- Nakatsu K, Loomis CW. Postanesthetic theophylline elimination (letter) 423
- Namiki A, see Nishikawa T
- Namnoum A, see Schieber RA
- Nancherla AR, Narang PK, Kim YD, Howard C, Gallelli JF, Clark RE, Macnamara TE. Sodium thiopental kinetics during cardiopulmonary bypass (abstract) S111
- Narang PK, see Nancherla AR
- Nath S, Häggmark S, Johansson G, Reiz S. Differential depressant and electrophysiologic cardiotoxicity of local anesthetics: an experimental study with special reference to lidocaine and bupivacaine 1263
- Naulty JS, see Datta S
- Nauss LA, see Gray JR
- Navalgund AA, Alifimoff JK, Jakymec AJ, Bleyaert AL. Amiodarone-induced sinus arrest successfully treated with ephedrine and isoproterenol 414
- Nemoto EM, see Levin LL
- Neuman GG, Baldwin CC, Petrini AJ, Wise L, Wollman SB. Perioperative management of a 430-kilogram (946-pound) patient with Pickwickian syndrome 985
- Newman CM, Lam AM. Induced hypotension for clipping of a cerebral aneurysm during pregnancy: a case report and brief review 675
- Newsome LR, Bramwell RS, Curling PE.

- Severe preeclampsia: hemodynamic effects of lumbar epidural anesthesia 31
- Roth JV, Hug CC Jr, Nagle D. Esmolol attenuates hemodynamic responses during fentanyl-pancuronium anesthesia for aortocoronary bypass surgery 451
- Nicholas DA, see Solanki DR
- Nicoll JMV, Treuren B, Acharya PA, Ahlen K, James M. Retrobulbar anesthesia: the role of hyaluronidase 1324
- Nicolson SC, Jobes DR. Arterial pressure monitoring during internal mammary artery harvesting (letter) 821
- Nigrovic V, Klaunig JE, Smith SL, Schultz NE, Wajskol A. Comparative toxicity of atracurium and metocurine in isolated rat hepatocytes 1107
- Nigrovic V. Preponderance of hydrolysis in inactivation of atracurium: questions remain (letter) 1368
- Niklason L, see Fletcher R
- Nishikawa T, Omote K, Namiki A, Takahashi T. The effects of nicardipine on cerebrospinal fluid pressure in humans 507
- Nishimura RA, see Abel MD
- Noda J, Umeda S, Mori K, Fukunaga T, Mizoi Y. Acetaldehyde syndrome after celiac plexus alcohol block 1300
- Nonoue T, see Sari A
- Norlén K, see Gorch T Jr
- Norman EA, Ahmad I, Zeig NJ. Delivery temperature of heated and cooled intravenous solutions 693
- Norman P, see Bruce DL
- North C, Marsh B, Hirshman CA. Anesthetic management of a patient with reactive airway disease for carbon dioxide laser debulking of a laryngeal tumor 1227
- Northrip DR, Bohman BK, Tsueda K. Total airway occlusion and superior vena cava syndrome in a child with an anterior mediastinal tumor 1079
- Nugent M, see Blaise GA
- Numata K, see Okazaki K
- O'Keefe MC. Thoughts on spinal anesthesia failures from a non-teaching hospital (letter) 317
- Ochs HR, see Greenblatt DJ
- Offord KP, see Fromme GA
- Ogasahara H, see Sari A
- Oh TH, Fox L, Kopf G. Systemic resistance and rewarming time following hypothermia for open heart surgery in infants: nitroprusside and/or droperidol (abstract) S112
- Kopf G. Does serum K⁺ level change after cardioplegia during cardiopulmonary bypass in pediatric open heart surgery (abstract) S113
- see Hannallah RS
- Okamoto K, see Komatsu T
- Okazaki K, Numata K, Fukunaga AF. The influence of the respiratory rate on the ratio of physiological dead space to tidal volume (abstract) S114
- Okumura F, see Furuya H
- Olson RA, see Lennon RL
- Olsson Y, see Gorch T Jr
- Olthof G, see Burm AGL
- Ominsky AJ, see Young ML
- Omote K, see Nishikawa T
- Ong BY, MacIntyre CJ, Bose D, Sitar D, Kozody R, Palahniuk RJ. Phenobarbital prevents loss of cerebral blood flow autoregulation after asphyxia in newborn lambs (abstract) S115
- Orfei P, see Rosa G
- Ornstein E, Matteo RS, Silverberg PA, Schwartz AE, Young WL. Dose-response relationship for vecuronium in the presence of chronic phenytoin therapy (abstract) S116
- see Matteo RS
- see Plotkin CN
- see Silverberg PA
- Orr RA, see Schieber RA
- Ostheimer GW, see Datta S
- Otagiri T, Sokoll MD. A microelectrode study of the effects of atracurium on neuromuscular transmission 345
- Otto CW, see Cork RC
- Owen H, see Kafer ER
- Owens EL, Kasten GW, Hessel EA II. Spinal subarachnoid hematoma after lumbar puncture and heparinization: a case report, review of the literature, and discussion of anesthetic implications 1201
- see Kasten GW
- Owens R, see Lippmann M
- Pace NL, see Bailey PL
- see Mock DL
- see Streisand JB
- Paganini EP, see Ghattas MA
- Pagden D, Halaburt AS, Wirpszo R, Karyn A. Posterior dislocation of the shoulder complicating regional anesthesia 1063
- Paicuis R, see Lippmann M
- Palacios I, see Mastrocostopoulos G
- Palahniuk RJ, see Bedder MD
- see Ong BY
- Paloheimo MPJ, see Cozanitis DA
- Pandya JB, Martin JT. Improved remote cardiorespiratory monitoring during radiation therapy 529
- Parker EO. Controlled drug accountability (letter) 539
- Parris WCV, Scott HW, Smith BE. Anesthetic management of system mastocytosis: experience with 42 cases (abstract) S117
- Paskin S, see Patel NJ
- Patel NJ, Flashburg MH, Paskin S, Grossman R. A regional anesthetic technique compared to general anesthesia for outpatient knee arthroscopy 185
- see Grant G
- Patterson MK, see Allen PD
- Paulus DA. Drilling remnants in elbow adapters (letter) 824
- Peachman FA, see Lee CM
- Pearson J, see Ebert J
- Pearson KS, Trawick DC, Jebson PJ. Early detection of experimental pulmonary edema in swine (abstract) S118
- Pedersen H. Anesthesia in obstetrics: maternal, fetal, and neonatal aspects (book review) 1374
- Pedersen NO, see Petring OU
- Pelligrino DA, see Becker GL
- Pendergrass TW, see Lynn AM
- Penning JP, Samson B, Baxter A. Nalbuphine reverses epidural morphine induced respiratory depression (abstract) S119
- Penny F, see Lam AM
- Perel A, Hoffman B, Podesh D, Davidson JT. High frequency positive pressure ventilation during general anesthesia for extracorporeal shock wave lithotripsy 1231
- Perkins FM, Howe JG, Stern P. Effect of postoperative epidural analgesia on resting metabolic rate (RMR) in man (abstract) S120
- see Stern P
- Pernick MS. A calculus of suffering (letter) 991
- Peterson DO, see Schubert A
- Peterson DR, Davis N. Malignant hyperthermia diathesis and sudden infant death syndrome (letter) 209
- Petit B, see Martin R
- Petring OU, Adelhof B, Jensen EN, Pedersen NO, Lomholt N. Prevention of silent aspiration due to leaks around cuffs of endotracheal tubes 777
- Petrini AJ, see Neuman GG
- Philbin DM, see Ramsay JG
- see Silbert BS
- Philip B, see Garfield JM
- Philpson EH, see Kuhnert BR
- Phythyon JM, see Wood M
- Piccione W Jr, see Butterworth JF IV

- Piehlér JM, see Weinlander CM
Pimental R, see Kuhnert BR
Pinsker MC. Anesthesia: a pragmatic construct (letter) 819
Pirak L, see Eisenkraft JB
Pittinger CB, Munson ES. Currency scores, medians, and half-lives (letter) 422
Plotkin CN, Ornstein E. Resistance to pancuronium: adult respiratory distress syndrome or phenytoin (letter) 820
Podch D, see Perel A
Pogrud H, see Drexler H
Poole GV Jr, see Prough DS
Port JD, see San Juan AC
Port M, see Matteo RS
Porter W, see Reitan JA
Possmayer F, see Enhorning G
Post C, see Gordh T Jr
Pototschnik R, see Enhorning G
Poulton TJ. Unusual corrugated tubing leak (letter) 1365
Prevoznik SJ. Handbook of regional anesthesia (book review) 106
Proctor J, see Vinik HR
Prough DS, Johnson JC, Stump DA, Poole GV Jr, Stullken EH. Cerebrovascular effects of rapid fluid resuscitation in a canine intracranial mass lesion model (abstract) S121
Kong D, Watkins WD, Stout R, Stump DA, Beamer WC. Inhibition of thromboxane A₂ production does not affect post-ischemic brain hypoperfusion in dogs (abstract) S122
Pucci WR, see Bedder MD
Puchi P, see Gallo JA
Puig M, Walsh J, Tang C, Lovitz M, Turndorf H. Premedication abolishes increase in plasma beta-endorphin due to presurgical stress (abstract) S123
Putnins CL, see Thomson IR
Pyles ST, see Berger JJ
see Berger JJ
Quinn ML, see Smith NT
Qureshi GD, see Fauss BG
Rabinov W, see Samuels SI
Racz GB, Heavner JE. Epidural phenol neurolysis using daily needle placements (letter) 822
Rafferty T, see Biondi J
Rah KH, see Fabian JA
Ramabadran K, Bansinath M. Naloxone-morphine synergism (letter) 1252
Ramanathan J, Bottorff M, Jeter JN, Khalil M, Sibai BM. The pharmacokinetics and maternal and neonatal effects of epidural lidocaine in preeclampsia 120
Khalil M, Chauhan D, Sibai B. Anesthetic management of "HELLP syndrome" in severe preeclampsia—a retrospective study (abstract) S124
Ramanathan S, Grant G, Turndorf H. Cardiac preload changes with ephedrine therapy for hypotension in obstetrical patients (abstract) S125
see Grant G
Ramsay JG, Arvieux CC, Foëx P, Philbin DM, Jeavons P, Ryder WA, Jones LA. Regional and global myocardial function in the dog when nitrous oxide is added to halothane in the presence of critical coronary artery constriction 431
Ramseur A, see Benzoin HT
Raphaely RC, see Finholt DA
Rees DI, Howell ML. Ketamine-atracurium by continuous infusion as the sole anesthetic for pulmonary surgery 860
see Gaines GY III
Rein P, see Moyer GA
Reitan JA, Porter W, Braunstein M. Comparison of psychomotor skills and amnesia after induction of anesthesia with midazolam or thiopental 933
see Kien ND
Reiz S, see Nath S
Renschler MF, see Cheng EY
Restifo R, see Hilavacek JR
Reves JG, see Flezzani P
see Henling CE
see Kates RA
see Samuelson PN
Reynolds WJ, see Kingsley CP
Rezkana H, see Ghattas MA
Rice P, Ethans CT. Difficult removal of epidural catheters in the sitting position (letter) 542
Richards TS, see Cohen JA
Rida WN, see Mark JB
Rietsema K, see Williams JP
Rinker RM, see Liao JC
Risbo A, see Banning A-M
Roaf E, see Garfield JM
Robblee JA, see Nadeau SG
Roberts AJ, see Cohen JA
Roberts FL, see Allee JL III
Roberts MM, see Ghattas MA
Robins DS. Safety of Lacri-Lube (letter) 1091
Robinson FP, see Dundee JW
Rodman J, Koehntop DE. Variability of fentanyl pharmacokinetics in neonates; reply (letter) 1370
see Koehntop DE
Rogol P, see Biondi J
Rojc K, see Estafanous FG
Romeo S, see Henning RJ
Ronai AK, see Avram MJ
see Shanks CA
see Sloan TB
Rooney SM, Howland WS. Acquired immune deficiency syndrome and anesthesia personnel (abstract) S126
Howland WS. Operative procedures associated with acquired immune deficiency syndrome complex (abstract) S127
Rorie DK, Tyce GM, Sill JC. Increased norepinephrine release from dog pulmonary artery caused by nitrous oxide 560
see Hunter LW
Rosa G, Orfei P, Sanfilippo M, Vilardi V, Gasparetto A. The effects of atracurium besylate on intracranial pressure and cerebral perfusion pressure 381
Rosen MA, see Daniels D
Rosenbaum SH, see Damask MC
Rosenberg H, Fletcher JE. Masseter muscle rigidity and malignant hyperthermia susceptibility 161
Rosenthal MH, see Cheng EY
Rosow CE, see Silbert BS
Ross WT, Arnold WP. Planning anesthesia services to support extracorporeal shock wave lithotripsy (abstract) S128
Roth JV, see Newsome LR
Rothstein P, Arthur GR, Feldman HS, Kopf GS, Covino BG. Bupivacaine for intercostal nerve blocks in children: blood concentrations and pharmacokinetics 625
Rouby JJ, see Brichant JF
Rous AC, see Coriat P
Roush JR, see Manchikanti L
Rousso M, see Drexler H
Rowlingson JC, Kirschenbaum LP. Epidural analgesic techniques in the management of cervical pain 938
see Grosslight KR
Rubin AP, see Kotob HIM
Rubin J, see Ivankovich AD
Runciman WB, see Mather LE
Rung GW, Schneider AJL. Oxygen flowmeter failure on the North American Drager Narkomed 2a anesthesia machine (letter) 211
Ruppreht J, Dworacek B. Cholinergic dysfunction and the anesthetic state (letter) 210
Ryder WA, see Ramsay JG
Sackellares C, see Samra SK
Saga-Rumley SA, see Berger JJ
Saidman LJ, see Schubert A
Saint-Maurice C, see Meistelman C
Sale JP, Goresky GV, Koren G, Strunin L. Pharmacokinetics of alfentanil in children (abstract) S129
Sale JP, see Maltby JR

- Salem MR, see Crystal GJ
 Salt PJ, see Klein J
 Samra SK, Vanderzant C, Sackellares C, Domer P. Differential effects of isoflurane on human central nervous system studies by median nerve evoked potentials (abstract) S130
 Samson B, see Penning JP
 Samuels SI, Rabinov W. Difficulty reversing drug-induced coma in a patient with sleep apnea 1222
 Shochat SJ. A new technique for stabilizing the oxygen saturation monitor probe in infants and children (letter) 213
 Samuelson PN, Reves JG, Kirklin JK, Bradley E Jr, Wilson KD, Adams M. Comparison of sufentanil and enflurane-nitrous oxide anesthesia for myocardial revascularization 217
 see Henling CE
 San Juan AC, Port JD, Wong KC. Hyperkalemia after dantrolene administration in dogs (abstract) S131
 Sanchala V, see Komatsu T
 Sanfilippo M, see Rosa G
 Sanford TJ Jr, Smith NT, Dec-Silver H, Harrison WK. A comparison of morphine, fentanyl, and sufentanil anesthesia for cardiac surgery: induction, emergence, and extubation 259
 see Smith NT
 Sari A, Matayoshi Y, Yonei A, Ogasahara H, Nonoue T, Yokota K, Yamashita S. Cerebral arteriovenous oxygen content difference during barbiturate therapy in patients with acute brain damage 1196
 Miyauchi Y, Yamashita S, Yokota K, Ogasahara H, Yonei A. The magnitude of hypoxemia in elderly patients with fractures of the femoral neck 892
 Sassoon CSH, see Baydur A
 Sathoff RH, see Spiess BD
 Sato K, see Kuribayashi H
 Sato Y, see Kuribayashi H
 Satwicz PR, see DiNardo JA
 Savarese JJ, see deBros FM
 see Goldhill DR
 see Scott RPF
 Scaf AHJ, see Bencini AF
 see Sohn YJ
 Scavone JM, see Greenblatt DJ
 Schaefer CF, Brackett DJ, Biber B, Lerner MP, Fagraeus L, Holaday JW, Wilson MF. Relative cardiorespiratory potency of the analeptic TRH under four anesthetics and in awake rats (abstract) S132
 Scheller MS, Drummond JC. Solubility of N₂O in volatile anesthetics contributes to vaporizer aberrancy when changing carrier gases 88
 Todd MM, Drummond JC, Zornow MH. A comparison of the ICP effects of isoflurane and halothane after cryogenic brain injury in rabbits (abstract) S133
 Scherb M, see Schou J
 Schieber RA, Namnoum A, Sugden A, Shiu GK, Orr RA, Cook DR. Hemodynamic effects of isoflurane in the newborn piglet: comparison with halothane 633
 Schmidt JF, see Banning A-M
 Schmidt SI, see Baysinger CL
 see Kingsley CP
 Schneider AJL, see Rung GW
 Schneider MJ, Stirt JA, Finholt DA. Atracurium, vecuronium, and intraocular pressure in humans 877
 Schou J, Scherb M. Postoperative sagittal sinus thrombosis after spinal anesthesia (letter) 541
 Schubert A, Drummond JC. The effect of acute hypocapnia on human median nerve somatosensory evoked responses (abstract) S134
 Drummond JC, Peterson DO, Todd MM, Shapiro HM. A comparison of CO₂ and bolus saline injection as tests of adequate Doppler placement in neurosurgery (abstract) S135
 Peterson DO, Drummond JC, Saidman LJ. The effect of high-dose fentanyl on human median nerve somatosensory evoked responses (abstract) S136
 Zornow MH, Drummond JC, Luerssen TG. Loss of cortical evoked responses due to intracranial gas during posterior fossa craniectomy in the seated position 203
 see Massion WH
 see Sohn YJ
 Schultetus RR, Hill CR, Dharamraj CM, Banner TE, Berman LS. Wakefulness during cesarean section after anesthetic induction with ketamine, thiopental, or ketamine and thiopental combined 723
 Schultz NE, see Nigrovic V
 Schur MS, see Kafer ER
 Schwartz AE, see Matteo R5
 see Ornstein E
 Schwartz AJ. Monitoring in anesthesia and critical care medicine (book review) 427
 Schwarz S, Agoston S, Houwertjes MC. Does intravenous infusion of nitroglycerin potentiate pancuronium- and vecuronium-induced neuromuscular blockade? 156
 see Bencini AF
 Scott EA, see Britt BA
 Scott HW, see Parris WCV
 Scott R, Savarese JJ, Basta SJ, Ali HH, Embree P. The clinical pharmacology of high dose atracurium (abstract) S137
 see deBros FM
 Scott W, see Biondi J
 Seldon TH. Harold Randall Griffith, MD, CM, FRCP(C), FFARCS(ENG), FRCS(C): 1894-1985 1051
 Serafini AN, see Szeinfeld M
 Serpico LC, see Kimovec MA
 Sethna DH, see Estafanous FG
 see Ghattas MA
 see Moffitt EA
 Shader RI, see Greenblatt DJ
 Shafer A, Sung M-L, White PF. Pharmacokinetics and pharmacodynamics of alfentanil infusions during general anesthesia 1021
 Shafer SL. The resident's friend (book review) 215
 Shaffer EA, see Maltby JR
 Shah A, see Young ET
 Shah K, Karlman R, Heller J. Ventricular tachycardia and hypotension with amniotic fluid embolism during cesarean section 533
 Shaheen O, see Wood M
 Shanks CA, Avram MJ, Kinzer J, Wilkinson CJ, Ronai AK, Judson P. Pharmacokinetics and pharmacodynamics of metocurine in cardiac surgery patients (abstract) S138
 see Avram MJ
 see Benzon HT
 see Carbone-Traber KB
 Shapiro BA, see Greene SJ
 Shapiro HM, see Schubert A
 Sharma M, see Cannon JE
 Shaw B, see Vinik R
 Shay S, see Wood M
 Sheiner LB, see Carpenter RL
 Shemin R, see Butterworth JF IV
 see Mark JB
 Shephard DAE, see Vandam LD
 Sheskey M, see Allen PD
 Shibusaki K, Komatsu T, Taddonio R, Lees DE. Rebound pulmonary artery hypertension following sodium nitroprusside induced hypotension (abstract) S139
 see Komatsu T
 Shimoji K, see Kuribayashi H
 Shin YK, Kim YD. Anesthetic considerations in patients receiving

- ritodrine therapy for preterm labor (abstract) S140
- Shiu GK, see Schieber RA
- Shocat SJ, see Samuels SI
- Shulman MS, see Wakerlin G
- Shutack JG. Pulmonary development, transition from intrauterine to extrauterine life (book review) 427
- Sibai B, see Ramanathan J
- Siegelman R, see Walter RR
- Silbert BS, Rosow CE, Keegan CR, Latta WB, Murphy AL, Moss J, Philbin DM. The effect of diazepam on induction of anesthesia with alfentanil 71
- Sill JC, see Rorie DK
- Silvay G, Dolman J, Zappula R, Mindich BP, Toth C, Erickson N, Kaplan JA. Effect of temperature, blood pressure, and cardiopulmonary bypass flow on evoked potential latency (abstract) S141
- Silver H, see Smith NT
- Silver MJ, see Howie MB
see Stock MC
- Silverberg PA, Matteo RS, Ornstein E, Young WL, Diaz J. Pharmacokinetics and pharmacodynamics of edrophonium in the elderly (abstract) S142
- Silverberg PA, see Ornstein E
- Silverman IM, see Vender JS
- Sipes IG, see Lind RC
see Moore RA
- Sitar D, see Ong BY
- Sivarajah S. Hepatic blood flow during controlled hypotension; reply (letter) 424
- Sivashankaran S, see Furgerson CL
- Sjöstrand UH, see Axelsson KH
- Skeehan TM, Hensley FA Jr. Axillary artery compression and the prone position (letter) 318
- Skourtis C, see Mastrocostopoulos G
- Sladen RN. Respiratory acidosis after cardiopulmonary bypass; reply (letter) 826
- Temperature correction of blood gas tensions?; reply (letter) 421
see Cheng EY
- Sleigh JW. Failure of aminophylline to antagonize midazolam sedation (letter) 540
- Sloan MS, see Spiess BD
- Sloan T, Ronai AK, Koht A. Reversible loss of somatosensory evoked potentials during anterior cervical spinal fusion 96
see Benzon HT
see Kirmovec MA
see Koht A
- Smerling A, Delphin E. A new device to smooth pediatric inhalation induction (letter) 1366
- Smith BE, see Parris WCV
- Smith G, Hines R, Barash P. Aortic cross-clamping: does it alter right ventricular function? (abstract) S143
- Hirsch N, Ehrenwerth J. Sight and sound: can double-lumen endobronchial tubes be placed accurately without fiberoptic bronchoscopy? (abstract) S144
- Smith JD, see Williams L
- Smith NT, Quinn ML, Westover CJ, Benthuisen JL, Silver H, Sanford TJ Jr. The EEGs of alfentanil, sufentanil, and fentanyl: a quantitative comparison (abstract) S145
- Westover CJ, Quinn ML, Benthuisen JL, Dec-Silver H, Sanford TJ Jr. Induction with thiopental or alfentanil: EEG effects (abstract) S146
see Sanford TJ Jr
- Smith P, see Fyman PN
- Smith SL, see Nigrovic V
- Smuckler EA, see Eger EI II
- Sohn YJ, Bencini AF, Scaf AHJ, Kersten UW, Agoston S. Comparative pharmacokinetics and dynamics of vecuronium and pancuronium in anesthetized patients 233
see Bencini AF
- Sokoll MD. Muscle relaxants: basic and clinical aspects (book review) 1095
see Mehta MP
see Otagiri T
- Solanki DR, Nicholas DA, Williams KR. Comparative effects of oral sodium citrate and oral cimetidine on gastric pH in pediatric patients (abstract) S147
- Sosis M. On the use of priming with vecuronium for rapid sequence induction (letter) 1367
- Broad T, Marr AT, Larijani GE. Comparison of atracurium with d-tubocurarine for prevention of succinylcholine myalgias (abstract) S148
- Marr AT, Larijani GE, Vekeman D. Priming with atracurium—a clinical trial (abstract) S149
- Spiersdijk J, see Burm AGL
- Spiess BD, Sathoff RH, El-Ganzouri ARS, Ivankovich AD. High-dose sufentanil: four cases of sudden hypotension on induction 703
- Sloan MS, Matz SD, Lubenow TR, Ivankovich AD. Incidence of venous air embolism in total hip arthroplasty (abstract) S150
- Spiss CK, Zadrobilek E, Weindlmayr-Goettel M, Draxler VH, Steinbereithner K. Nifedipine induced hypotension in man: endocrine response during isoflurane and halothane anesthesia (abstract) S151
- Sprague DH, Maccioli GA. Disposable circuit tubing melted by heated humidifier (letter) 1247
- Stack RS, see Kates RA
- Standaert FG, see Goudsouzian NG
- Stanley JC, see Hantler CB
- Stanley TH, see Bailey PL
see Mock DL
see Streisand JB
see Williams JP
- Staples ED, see Cohen JA
- Starr NJ, see Estafanous FG
- Steinbereithner K, see Spiss CK
- Steinbrook RA, see Mark JB
- Stern P, Howe JG, Perkins FM. Effect of epidural anesthesia on resting metabolic rate (abstract) S152
see Datta S
see Perkins FM,
- Steubing R, see Hagenouw RRPM
- Stevens WC, see Graham TM
- Stevenson JB, see Fujinaga M
- Steward DJ. Comments on the review of manual of pediatric anesthesia (letter) 1368
see Britt BA
- Stewart RD, see Williams RT
- Stiles CM, see Baydur A
- Stiller R, see Cook DR
- Stirt JA, see Finholt DA
see Minton MD
see Schneider MJ
- Stock MC, McDonald JS, Silver MJ, Downs JB. How fast does CO₂ really rise during apnea? (abstract) S153
- Stocking-Korzen R, see Streisand JB
- Stolz S, Couture LJ, Edmonds HL Jr. Evidence of partial recall during general anesthesia (abstract) S154
see Couture LJ
- Stone D, see Hilavacek JR
- Stout D, Dwersteg J, Cullen BF, Bishop MJ. Correlation of endotracheal tube size with sore throat and hoarseness following general anesthesia (abstract) S155
- Stout R, see Prough DS
- Stowe DF, see Bosnjak ZJ
- Streisand JB, Clark NJ, Stanley TH, Pace NL, Gillmor ST, de Jong P, Hilkens P, Stocking-Korzen R, de Vries C. The effects of technique and supplements on cardiovascular dynamics during anesthetic induction with alfentanil (abstract) S156
see Mock DL
- Striker TW, see Adler E

- Strunin L, see Sale JP
 Stuart S, see McGarrigle RE
 Stuebing RC, see Thompson GA
 Stullken EH, see Prough DS
 Stump DA, see Prough DS
 Su JY, Bell JG. Intracellular mechanism of action of isoflurane and halothane on striated muscle of the rabbit 457
 see Caplan RA
 Suddarth LT, see Finholt DA
 Sugden A, see Schieber RA
 Sullivan JA, see Imrie DD
 Sullivan KB, Kapur PA. The effect of beta-adrenergic blockade on the cardiovascular response to diltiazem or verapamil in dogs 1099
 Sundberg AEA, see Axelsson KH
 Sung M-L, see Shafer A
 Sutherland AD, Williams RT. Cardiovascular responses and lidocaine absorption in fiberoptic-assisted awake intubation 389
 see Maltby JR
 Swedlow DB, see Gibbons PA
 Sweetman BJ, see Wood M
 Swerdlow BN, Mihm FG, Goetzel EJ, Matthay MA. Leukotrienes in pulmonary edema fluid after cardiopulmonary bypass 306
 Sykes MK. Nuffield Department of Anaesthetics, Oxford (letter) 211
 Syracuse CD, see Kuhnert BR
 Szeinfeld M, Serafini AN, Heal A, Machado R, Lurie CR. Epidural blood patch: direction of the needle bevel and spread of blood injected into the epidural space (abstract) S157
 Sznajder JJ, see Breen PH
 Szyfelbein SK, see Hagen J
 Taddonio R, see Shibutani K
 Tajik AJ, see Abel MD
 Takahashi H, see Matsumiya N
 Takahashi T, see Nishikawa T
 Takeshima R, see Dohi S
 Talmage EA. Inherent safety of Racz catheters (letter) 821
 Tan S, Cohen SE, White PF. Sufentanil for analgesia after cesarean section: intravenous vs epidural administration (abstract) S158
 Tanaka A, see Matsumoto M
 Tang C, see Puig M
 Tanguy A, see Dalens B
 Tasch MD, see Kim KC
 Taylor PC, see Ghattas MA
 Teddy PJ, see Jamous MA
 Teunissen E, see Williams JP
 Themann H, see Van Aken H
 Thiagarajah S, Grynstejn M, Lear E, Azar I. Ventricular arrhythmias after terbutaline administration to patients anesthetized with halothane 417
 Thomas RD, Behbehani MM, Coyle DE, Denson DD. Cardiovascular toxicity of local anesthetics: an alternative hypothesis 444
 Thompson GA, Turner PA, Bridenbaugh PO, Stuebing RC, Denson DD. The influence of diazepam on the pharmacokinetics of intravenous and epidural bupivacaine in the rhesus monkey 151
 see Denson DD
 Thomson IR, Putnins CL, Friesen RM. Hyperdynamic cardiovascular responses to anesthetic induction with high-dose fentanyl 91
 Thorburn JR, James MFM, Feldman C, Moyes DG, Du Toit PS. Comparison of the effects of atropine and glycopyrrolate on pulmonary mechanics in patients undergoing fiberoptic bronchoscopy 1285
 Thys DM, Hillel Z, Mindich BP, Goldman ME, Kaplan JA. Halothane is a potent myocardial depressant during fentanyl anesthesia (abstract) S159
 see Cohen E
 see Eisenkraft JB
 see Hillel Z
 see Konstadt SN
 Tippitt SE, see Kapur PA
 Todd G, see Damask MC
 Todd MM. Head injury and the anaesthetist (book review) 1095
 see Scheller MS
 see Schubert A
 Toleikis JR, see Benzon HT
 Toth C, see Eisenkraft JB
 see Silvay G
 Toung TJK, Donham RT, Chen CT. Topical tracheal anesthesia can be administered through a catheter attached to the endotracheal tube (letter) 315
 McPherson RW, Ahn H, Donham RT, Alano J, Long D. Pneumocephalus: effects of patient position on the incidence and location of aerocele after posterior fossa and upper cervical cord surgery 65
 Townes BD, Dikmen SS, Biedsoe SW, Hornbein TF, Martin DC, Janesheski JA. Neuropsychological changes in a young healthy population after controlled hypotensive anesthesia 955
 Tran DQ. Cost of muscle relaxant drugs: other factors to be considered (letter) 422
 Trawick DC, see Pearson KS
 Tremper KK, Barker SJ. Basic physics and measurements in anesthesia (book review) 1372
 see Barker SJ
 Treuren B, see Nicoll JMV
 Triantafillou AN, Tsueda K, Berg J, Wieman TJ. Refractory bradycardia after reversal of muscle relaxant in a diabetic with vagal neuropathy 1237
 Trouwborst A, see Klein J
 Tsai SK, Mok MS, Lee TY, Chen WS, Li CC, Lee C. The priming effect of vecuronium in children (abstract) S160
 see Mok MS
 Tsueda K, see Northrip DR
 see Triantafillou AN
 Tulchinsky D, see Datta S
 Turnage G, see Waldman SD
 Turndorf H, see Grant G
 see Puig M
 see Ramanathan S
 see Vaida GT
 Turner PA, see Thompson GA
 Turunen MT, see Hynynen MJ
 Tuttle DB, see Hantler CB
 Tweed WA, see Murkin JM
 Twerskey RS, Kaplan JA. Junctional rhythm in a patient with mitral valve prolapse 975
 Tyce GM, see Hunter LW
 see Rorie DK
 Tydén H, see Fletcher R
 Uetrecht J, see Wood M
 Umeda S, see Noda J
 Unadkat JD, see Carpenter RL
 Ünal N, see Gürel A
 Upton RN, see Mather LE
 Uram M, see Levin LL
 Urmey WF, Lambert DH. Spinal anesthesia associated with reversal of myocardial ischemia 908
 Usta N, see Baraka A
 Vaes L, see Van Zundert A
 Vaida GT, Moss P, Capan LM, Turndorf H. Prolongation of lidocaine spinal anesthesia with phenylephrine 78
 Van Aken H, Fitch W, Graham DI, Brussel T, Themann H. Cardiovascular and cerebrovascular effects of isoflurane-induced hypotension in the baboon 565
 Van der Aa P, see Van Zundert A
 Van der Donck A, see Van Zundert A
 Van Egmond J, see Hagenouw RRP
 Van Etten A, see Bloor BC
 Van Kleef JW, see Burm AGL
 Van Rheineck Leyssius AT, Kalkman CJ, Bovill JG. Influence of moderate hypothermia on posterior tibial nerve somatosensory evoked potentials 475
 Van Zundert A, Vaes L, Van der Aa P, Van der Donck A, Meeuwis H.

- Motor blockade during epidural anesthesia 333
- Vaes L, Van der Aa P, Van der Donck A, Meeuwis H. RAM testing in obstetric patients (letter) 1245
- Vandam LD, Shephard DAE. Cushing's contributions to anesthesia: two comments (letter) 1249
- Vanderzant C, see Samra SK
- Varma S, see Galloway FM
- Vazeery Ak, see Badrinath S
- Vekeman D, see Sosis M
- Vender JS, Matthew EB, Silverman IM, Konowitz H, Dau PC. Heparin-associated thrombocytopenia: alternative managements 520
- Verespej J, see Lippmann M
- Veselis RA, see Lynch C III
- Viars P, see Brichant JF
see Chauvin M
see Coriat P
see Fusciardi J
- Vigváry Z, see Hamar O
- Vilardi V, see Rosa G
- Vinik HR, Gelman S, Proctor J, Halpern NB. Computerized infusion of sufentanil: a comparison of morbidly obese and nonobese patients (abstract) S161
see Gregoretti S
- Vinik R, Shaw B, Harris C, Maness R. Randomized evaluation of induction and recovery from anesthesia with diprivan or thiopental sodium (abstract) S162
- Volgyesi GA, see James PD
- Wade LD, see Wong HY
- Wajskol A, see Nigrovic V
- Wakefield TW, see Hantler CB
- Wakerlin G, Shulman MS, Yamaguchi LY, Brodsky JB, Mark JBD. Experience with lumbar epidural hydromorphone for pain relief after thoracotomy (abstract) S163
- Waldman SD, Feldstein GS, Allen ML, Turnage G. Selection of patients for implantable intraspinal narcotic delivery systems 883
see Feldstein GS
- Walker WE, see Williams JP
- Walman T, see Allen PD
- Walmsley AJ, Giesecke AH, Lipton JM. Epidural temperature: a cause of shivering during epidural anesthesia (abstract) S164
- Walsh J, see Puig M
- Walter RR, Kim YD, Macnamara TE, Katz NM, Siegelman R. Comparison of isoforane vs fentanyl anesthesia in ligation of the patent ductus arteriosus in preterm infants (abstract) S165
- Wang JJ, see Mok MS
- Wang JK, see Gray JR
- Ward RJ, see Birmingham PK
- Waters SJ, see Lind RC
- Watkins WD, see Konstadt SN
see Prough DS
- Watson WJ. Fentanyl and fertilization (letter) 103
- Waud BE, Waud DR. Tubocurarine sensitivity of the diaphragm after limb immobilization 493
- Waud DR, see Waud BE
- Weber S, Muravchick S. Electrical and mechanical train-of-four responses during depolarizing and nondepolarizing neuromuscular blockade 771
- Weindlmayr-Goettel M, see Spiss CK
- Weinlander CM, Abel MD, Piehler JM. Spontaneous cardiac herniation after pneumonectomy 1085
- Weintraub HD. Anesthesia for ambulatory surgery (book review) 997
- Weiss JB, see Datta S
- Weissman C, see Damask MC
- Wells J, see Kotob HIM
- Westman HR. Anesthesiology—a manual for medical students (book review) 107
- Westover CJ, see Smith NT
- Westphal LM, see Doze VA
- Wetmore RE, see Goode JG
- Wetzel RC, Marsh BR, Yaster M, Casella JF. Anesthetic implications of protein C deficiency 982
- Wheeler AS. The pregnant surgical patient (book review) 549
- White DA, see Kien ND
- White PF. Pharmacologic and clinical aspects of preoperative medication 963
see Doze VA
see Shafer A
see Tan S
- Whitehouse WM, see Hantler CB
- Widman GB, see Axelsson KH
- Wieman TJ, see Triantafillou AN
- Wignes M, see Murray MJ
- Wilkinson CJ. The heart: physiology, metabolism, pharmacology, and therapy (book review) 1253
see Shanks CA
- Williams JP, McArthur JD, Walker WE, Teunissen E, Rietsema K, Stanley TH. The cardiovascular effects of propofol in patients with impaired cardiac function (abstract) S166
- Williams KR, see Solanki DR
- Williams L, Barton C, McVey JR, Smith JD. A visual warning device for improved safety (letter) 1364
- Williams RT, Stewart RD. Transillumination of the trachea with a lighted stylet (letter) 542
see Sutherland AD
- Williams WT, Lowry RL, Eggers GWN. Anesthetic management during therapeutic disruption of the blood-brain barrier 188
- Wilson CM, Dundee JW, Moore J. Plasma midazolam levels in non-pregnant and parturient women (abstract) S167
- Wilson KD, see Samuelson PN
- Wilson MF, see Schaefer CF
- Wilton NCT, Globerson JH, de Rosayro AM. Epidural blood patch for postdural puncture headache: it's never too late 895
- Winter PM, see Levin LL
- Wirpszo R, see Pagden D
- Wise L, see Neuman GG
- Wojtczak JA, Kaplan JA. Negative inotropic effects of bupivacaine in isolated cardiac muscle mechanisms and reversal (abstract) S168
- Wollman SB, see Neuman GG
- Wong HY, Lichtenthal PR, Wade LD. The effect of anesthetic techniques on perioperative fluid requirement during coronary artery bypass surgery (abstract) S169
- Wong KC, see San Juan AC
- Wood AJJ, see Wood M
- Wood LDH, see Breen PH
- Wood M. Plasma drug binding: implications for anesthesiologists 786
- Uetrecht J, Phythyon JM, Shay S, Sweetman BJ, Shaheen O, Wood AJJ. The effect of cimetidine on anesthetic metabolism and toxicity 481
- Workhoven MN. Intravenous fluid temperature, shivering, and the parturient 496
- Woronowicz A, see Braverman B
- Wren WS, McShane AJ. Induction of anesthesia with isoflurane in children (letter) 365
- Wu C-H, see Kien ND
- Yaksh TL, see Durant PAC
- Yamaguchi H, see Ishizawa Y
- Yamaguchi LY, see Wakerlin G
- Yamashita S, see Sari A
- Yanagi T, see Murakawa K
- Yaster M, see Wetzel RC
- Yokota K, see Sari A
- Yonei A, see Sari A
- Young ET, Goudsouzian NG, Shah A. Effect of ranitidine on intragastric pH in children (abstract) S170
see Goudsouzian NG
- Young ML, Ominsky AJ. A simple aid to blind tracheal intubation (letter) 825
- Young WL, see Matteo RS
see Ornstein E
see Silverberg PA
- Youngberg JA. Recent advances in

- anaesthesia and analgesia (book review) 324
- Younker D, Jones MM, Adenwala J, Citrin A, Joyce TH III. Maternal cortical vein thrombosis and the obstetric anesthesiologist 1007
- Yuge O, see Matsumoto M
- Zaccari J, see Barker SJ
- Zadrobilek E, see Spiss CK
- Zaidan JR, Johnson S, Brynes R, Monroe S, Guffin AV. Rate of protamine administration: its effect on heparin reversal and antithrombin recovery after coronary artery surgery 377
- see Levy JH
- Zappula R, see Silvay G
- Zauder HL, see Hirsch IA
- Zeig NJ, see Norman EA
- Zorn GL, see Henling CE
- Zornow MH, see Scheller MS
- see Schubert A
- Zuspan KJ, see Kuhnert BR

Subject Index

- AIDS**, see Infection, acquired immune deficiency syndrome
- Acquired immune deficiency syndrome**, see Infection
- Alcohol**
celiac plexus block 1300
- Alfentanil**, see Analgesics
- Analgesics**
Anesthetics, intravenous
- Allergy**
protamine 739
- Alphaprodine**, see Analgesics
- Aminophylline**, see Pharmacology
- Amiodarone**, see Heart, arrhythmias
- Amniotic fluid**, see Anesthesia, obstetric
- Embolism**
- Ampules**, see Equipment
- Amrinone**, see Pharmacology
- Amulatory**, see Anesthesia, outpatient
- Analgesics**
alfentanil
common bile duct pressure with 370
diazepam effect on induction 71
distribution in CSF, blood and lymph with epidural injection 583
fentanyl compared to (abstract) S145
hemodynamic responses with halothane anesthesia 765
hepatic plasma flow effect on plasma concentrations of 999
induction technique affecting cardiovascular dynamics (abstract) S156
pharmacokinetics and pharmacodynamics of 1021
pharmacokinetics in children (abstract) S129
pharmacokinetics in parturient women 1155
placental transfer of 1155
spinal cord neuron effects of 145
sulfentanil compared to (abstract) S145
alphaprodine
neonatal responses during labor 392
butorphanol
dezocine compared to 283
potencies of (letter) 1246
control systems for (letter) 539
dezocine
butorphanol compared to 283
potencies of (letter) 1246
fentanyl
administration in lollipop form (abstract) S102
alfentanil compared to (abstract) S145
clinical and physiologic effects (abstract) S55
common bile duct pressure with 370
etomidate anesthesia with 979
fertilization and (letter) 103
hemolysis after 207
morphine comparison for cardiac surgery 259
pharmacokinetics in neonates 227; (letter) 1369
reproductive and teratogenic effects (abstract) S52
sufentanil compared to 259; (abstract) S145
thiopental interactions with 1149
heroin
epinephrine effects on 1290
intrathecal administration of 718
hydromorphone
for post-thoracotomy pain relief (abstract) S163
meperidine
normeperidine toxicity 536
morphine
cisternal cerebrospinal fluid concentrations after intramuscular administration (abstract) S31
fentanyl comparison for cardiac surgery 259
halothane interactions with (letter) 319
intrathecal administration of 718, 873
nalbuphine antagonism of 615
naloxone interactions with (letter) 313, 1252
oral controlled release vs epidural administration 385
pentobarbital antinociceptive interaction with 601
postoperative pain relief, anorectal surgery and 499
postoperative pain relief, epidural administration and 165
postoperative pain relief, thoracotomy and, 873
sufentanil comparison for cardiac surgery 259
thiopental interactions with 1149
nalbuphine
clinical and physiological effects (abstract) S55
respiratory depression reversed by (abstract) S19, S119
somatosensory-evoked potentials affected by (abstract) S51
narcotic
implantable intraspinal delivery systems for 883
spinal cord neuron effects of 145
sufentanil
alfentanil compared to (abstract) S145
computerized infusion in obese vs nonobese patients (abstract) S161
enflurane-nitrous oxide anesthesia compared to 217
fentanyl compared to 259; (abstract) S145
intravenous vs epidural
administration for cesarean section (abstract) S94
morphine for cardiac surgery compared to 259
somatosensory-evoked potentials affected by (abstract) S81
- Anatomy**
coronary circulation 294
spinal canal, epidural space 747
spinal nerve root 325
- Anesthesia**
cardiovascular
aortic cross-clamping and right ventricular function in (abstract) S143
arterial pressure monitoring during (letter) 821
arterial vs peak end tidal partial pressure of CO₂ during surgery (abstract) S41
blood pressure readings during and after (letter) 827
calcium channel blockers and beta blockers with 905
complement activation and (abstract) S90
coronary circulation and 294
cortisol response to cardiopulmonary bypass with 1117
early extubation effect on shunt after coronary artery bypass (abstract) S35
enflurane-nitrous oxide vs sufentanil 217
esmolol effects on
fentanyl-pancuronium anesthesia 451
evoked potential latency affected by (abstract) S141
fentanyl anesthesia with lidocaine for 511
fentanyl-enflurane for coronary arterial surgery 46
fluid requirements for (abstract) S169
for Fontan procedure 516
general vs epidural for femoral-popliteal bypass surgery (abstract) S39
heparin-associated thrombocytopenia and 520
hypertensive patients affected by (abstract) S75
isoflurane for coronary arterial surgery 53
isoflurane vs fentanyl in infants (abstract) S165

- ketanserin management of carcinoid tumor and 809
- lidocaine effect on ventricular defibrillation 337
- morphine, fentanyl and sufentanil compared for 259
- myocardial oxygenation in coronary artery disease and 395
- opiates for 259
- oxygen-hemoglobin affinity changes (abstract) S92
- pediatric (abstract) S112, S113, S165
- percutaneous transluminal coronary angioplasty and 815
- postoperative potassium requirements (abstract) S77, S78
- protamine reaction risk evaluation 739
- respiratory acidosis after (letter) 825
- slow channel calcium blocker effect on platelet function (abstract) S66
- temperature and somatosensory evoked responses (abstract) S85
- verapamil treatment of ventricular arrhythmia during (letter) 102
- definition of (letter) 819
- geriatric
- hypoxemia with femoral neck fractures and 892
 - midazolam induction for 15
 - propofol sensitivity (abstract) S43
- neurosurgical
- induced hypotension for clipping of cerebral aneurysm and 675
 - physostigmine reversal of general anesthesia for neurologic testing 1059
 - reversible loss of somatosensory evoked potentials during 96
- obstetric
- alfentanil pharmacokinetics in 1155
 - alphaprodine administration and, 392
 - amniotic fluid embolism and 533
 - bupivacaine-induced cardiovascular toxicity and 341
 - 2-chloroprocaine half-life and, 273
 - cortical vein thrombosis and 1007
 - general vs epidural, for cesarean delivery (abstract) S104
 - hypotension and 675; (abstract) S125
 - intrathecal morphine for patient with cystic fibrosis 1357
 - ketamine, thiopental, or ketamine-thiopental combined 723
 - lidocaine, disposition in mother, fetus and neonate 139
 - lidocaine, labor and (abstract) S30
 - lidocaine, preeclampsia and 120
 - management of HELLP syndrome (abstract) S124
 - motor blockade during epidural anesthesia 333
 - myotonia dystrophica and 687
 - postpartum tubal ligation and 897
 - preeclampsia and 31, 120
 - progesterone concentrations and 950
 - pulse rate changes during epidural anesthetic test doses (letter) 1089
 - RAM testing and (letter) 1245
 - ritodrine therapy and (abstract) S140
 - uterine displacement device and (letter) 424
- ophthalmologic
- retrobulbar, hyaluronidase in 1324
- orolaryngologic
- carbon dioxide laser debulking of laryngeal tumor and 1225
- orthopedic
- general vs regional techniques compared 185
 - hemodilution and blood transfusion for spinal fusion patient (abstract) S76
 - halothane and isoflurane anesthesia for children 181
 - preoperative oral fluids for 1112
 - propofol vs methohexital for 1189
- pediatric
- book review comments (letter) 1368
 - bupivacaine intercostal nerve blocks 625
 - device for smoothing inhalation induction (letter) 1366
 - fentanyl management for hypoplastic left heart syndrome repair 127
 - fentanyl pharmacokinetics for 227; (letter) 1369
 - for Fontan procedure 516
 - gas exchange during controlled ventilation and 645
 - halothane and isoflurane anesthesia for outpatient procedure 181
 - hypoxemia after 267
 - isoflurane induction in newborn piglets, 633
 - isoflurane induction (letter) 1365
 - lidocaine, cardiovascular effects of caudal administration 1074
 - lidocaine, pharmacokinetics during general anesthesia 279
 - mediastinal tumors and 1079
 - myoneural junction in 1208
 - neuromuscular function recovery after atracurium 1042
 - operative and postoperative pain relief 1069
 - oxygen saturation during tracheal intubation (abstract) S58
 - pancuronium, metocurine effects and 1340
 - pancuronium, pharmacokinetics and pharmacodynamics of 1319
 - succinylcholine effects on heart rate and rhythm 1329
 - tourniquet release in 865
 - vecuronium pharmacokinetics and pharmacodynamics 1319
- thoracic
- cardiac herniation after pneumonectomy and 1085
 - mediastinal tumors and 1079
 - oxygen and halothane entrainment during jet ventilation 191
- urologic
- extracorporeal shock wave lithotripsy and 1231; (abstract) S128
- Anesthesiologists**
- back pain as an occupational hazard (abstract) S13
- Anesthetic techniques**
- endobronchial
 - fiberoptic endoscope usage (abstract) S144 - epidural
 - alfentanil pharmacokinetics in 1155
 - blood patch, deafness and 312
 - blood patch, postdural puncture headache treatment via 895
 - carbon dioxide response with cervic thoracic block 9
 - catheter removal in sitting position (letter) 542
 - cervical pain management via 938
 - diacetylmorphine and 1290
 - epinephrine effects on 1281, 1290
 - ketamine for postoperative pain (letter) 989
 - lidocaine, labor and (abstract) S30
 - lidocaine, pH-adjusted solutions for 760
 - lidocaine, preeclampsia and 113
 - mechanism of differential block 325
 - morphine, anorectal surgery and 49
 - morphine, bupivacaine and 1033
 - morphine, distribution in CSF, blood and lymph 583
 - morphine, postoperative pain relief via 165
 - morphine, chronic pain relief via 53
 - motor blockade during 333
 - myocardial infarct size after coronary artery occlusion with 711
 - narcotics and (abstract) S105
 - operative and postoperative pain relief via 1069
 - phenol neurolysis using daily needle placement (letter) 822
 - preeclampsia and 31, 113
 - RAM testing and (letter) 1245
 - Racz catheters for (letter) 821
 - resting metabolic rate and (abstract) S120, S152
 - shivering and (abstract) S164
 - spread of blood into epidural space (abstract) S157 - hypotensive
 - bis-trimethaphan nitroprusside and (abstract) S33
 - clonidine effect on sympathoadrenal response during 469
 - hepatic blood flow during (letter) 422
 - isoflurane-induced hypotension 565, 660
 - neuropsychological changes resulting from 955
 - orthognathic surgery and 683

Anesthetic techniques—continuedhypotensive—*continued*

- rebound pulmonary artery hypertension and (abstract) S139

intravenous

- alfentanil pharmacokinetics and 1155
- ketamine-atracurium continuous infusion and 860
- low-dose anesthesia for hand surgery 812

regional

- brachial plexus block (letter) 44
- bupivacaine intercostal nerve blocks 625
- celiac plexus block (letter) 1092
- cocaine or lidocaine block of sphenopalatine ganglion 700
- general anesthesia for knee arthroscopy vs 185; (letter) 1091
- low-dose anesthesia for hand surgery 812
- posterior dislocation of shoulder and 1063
- retrobulbar 1324
- ulnar nerve block 843

spinal

- adrenergic agonist effect on venous return during 612
- bupivacaine subarachnoid administration 753
- caffeine administration for postdural puncture headache (letter) 316
- failures of (letter) 317
- glass particle contamination in ampules for 1361
- hearing loss after 312
- lidocaine, delayed cephalad spread of 523
- lidocaine, disposition in mother, fetus and neonate 139
- lidocaine, phenylephrine and 781
- lidocaine, vasoconstrictors and 365
- morphine, heroin and 718
- morphine, post-thoracotomy pain relief via 873
- myocardial ischemia reversal with 908
- opioid agonist and respiratory depression (abstract) S28
- position and spread of solutions (letter) 314
- postdural puncture headache management and 316, 1242
- postpartum tubal ligation and 897
- progesterone concentrations and 950
- sagittal sinus thrombosis after (letter) 541
- selective kappa opioid agonist for 350
- tetracaine effects prolonged in dogs (abstract) S14
- tourniquet pain and 1181

topical

- administration through catheter attached to endotracheal tube (letter) 315

Anesthetics, gases

nitrous oxide

- hemodynamic effects, halothane anesthesia and 765
- hemodynamic effects, in infants (abstract) S67
- intracranial pressure and 65
- midazolam interaction with 729
- norepinephrine release from pulmonary artery and 560
- oxygen consumption and 355
- platelet aggregation and 1170
- pneumocephalus incidence and 65
- pulmonary vascular responses in newborn lambs 62
- solubility in volatile anesthetics as factor in vaporizer aberrancy 88
- sufentanil compared to enflurane; nitrous oxide anesthesia 217

Anesthetics, intravenous

alfentanil

- diazepam effect on 71
- hepatic plasma flow effect on plasma concentrations of 999
- pharmacokinetics and pharmacodynamics of 1021

diazepam

- alfentanil induction affected by 71
- baroreflex and catecholamine responses 113

etomidate

- electroencephalogram effects of 1004
- fentanyl anesthesia with 979
- prolonged myoclonus after (letter) 992

fentanyl

- cardiovascular responses to 91
- cortisol response to surgery with 1117
- hemodynamic responses during coronary arterial surgery 46
- hypoplastic left heart syndrome repair and 127
- myocardial ischemia prevention with 617
- myocardial metabolism during coronary arterial surgery 46
- myocardial salvage after coronary artery occlusion with (abstract) S50
- somatosensory-evoked responses and (abstract) S136

ketamine

- acute epiglottitis management with (abstract) S3
- atracurium continuous infusion with 860
- epidural administration for postoperative pain (letter) 989
- low intensity tactile sensory input and 1123
- thiopental compared and combined with 723

methohexital

- propofol vs 1189
- midazolam

baroreflex and catecholamine responses 113

narcotics for cardiac surgery 259

propofol

- cardiovascular effects with impaired cardiac function (abstract) S166
- geriatric sensitivity to (abstract) S43
- methohexital compared to 1189

sufentanil

- enflurane-nitrous oxide anesthesia compared to 217

thiopental

- cardiopulmonary bypass and (abstract) S111
- cerebral evoked potentials affected by (abstract) S80
- epinephrine-induced dysrhythmias and 437; (abstract) S8
- ketamine compared and combined with 723
- morphine and fentanyl interactions with 1149
- psychomotor skills and amnesia after induction 933

Anesthetics, local

bupivacaine

- cardiac dysrhythmias induced by 133
- cardiovascular toxicity of 341, 444, 1029, 1263
- diazepam effects on pharmacokinetics of 151
- epinephrine effects on 1281
- glucose addition to 1181
- intercostal nerve blocks in children 625
- myocardial contractility depression by 551, 1263
- negative inotropic effects of (abstract) S168
- postpartum tubal ligation and 897
- sinoatrial nodal effects of 911
- subarachnoid administration effect on venous blood concentrations 753
- central nervous system toxicity of 840

2-chloroprocaine

half-life of 273

cocaine

- sphenopalatine ganglion block via 700

etidocaine

- myocardial contractility depression by 551

lidocaine

- cardiac dysrhythmias induced by 133
- cardiovascular toxicity of 444, 1074
- depressant and electrophysiologic cardiotoxicity of 1263
- epinephrine and 1074, 1281
- fentanyl anesthesia with 511
- hemodynamic effects with rapid sequence induction 1037
- hepatic and renal clearances of 943
- maternal, fetal and neonatal disposition of 139

- myocardial contractility depression by 551
 pH-adjusted solutions for epidural anesthesia 760
 pharmacokinetics, preeclampsia and 120
 pharmacokinetics, pediatric 279
 phenylephrine prolongation of 781
 sinoatrial nodal effects of 911
 sphenopalatine ganglion block via 700
 spinal anesthesia with delayed cephalad spread 523
 vasoconstrictor effect on 365
 ventricular defibrillation effect of 337
 maternal and neonatal platelet function affected by (abstract) S63
 procaine
 cardiac dysrhythmias induced by 133
- Anesthetics, volatile**
 chloroform
 pulmonary surfactant films affected by 1275
 enflurane
 amrinone and 849
 cimetidine and 481
 diltiazem and 918
 hepatotoxicity of 21; (letter) 545
 myocardial metabolism during coronary arterial surgery 46
 naloxone and 330
 nitrous oxide solubility in 88
 pharmacokinetics, comparative 575
 sufentanil compared to enflurane-nitrous oxide 217
 thiopental and epinephrine-induced dysrhythmias with 437
 ether
 pulmonary surfactant films affected by 1275
 halothane
 behavioral effects of chronic exposure to 653
 cigarette smoke effect on 37
 cimetidine effect on 481
 fentanyl anesthesia and (abstract) S71
 hepatotoxicity of (editorial) 831
 hepatotoxicity of, genetic predisposition to 1143
 hepatotoxicity of (letter) 545
 high energy phosphate levels and 1130
 lidocaine hepatic and renal clearance with 943
 mechanism of action on striated muscle of rabbit 457
 metabolism in acyanotic and cyanotic patients 1257
 morphine interactions with (letter) 319
 myocardial depressant effects of (abstract) S71, S159
 myocardial function effects with coronary artery disease 431
 naloxone and 330
 nitrous oxide solubility in 88
 norepinephrine uptake in canine saphenous veins with 360
 partial pressure effects on solubility in blood 672, 960
 pediatric, induction (letter) 1365
 pediatric, outpatient anesthesia 181
 pharmacokinetics, comparative 575
 pulmonary surfactant films affected by 1275
 reductive defluorination of 835
 sufentanil and hemodynamic effects of (abstract) S93
 synaptosomal acetylcholine metabolism and (letter) 103
 verapamil interactions with 463
- isoflurane
 atracurium pharmacokinetics and pharmacodynamics with 743
 cardiovascular and cerebrovascular effects of 565
 central nervous system effects of (abstract) S130
 cerebral blood flow and 660; (abstract) S6, S107
 coronary artery response to phenylephrine and prostaglandins (abstract) S20
 cortisol response to cardiopulmonary bypass with 1117
 diltiazem and 81
 EEG patterns, (abstract) S107
 EEG patterns, pediatric cardiac operations and 525
 EMG response to auditory stimuli (abstract) S36
 hemodynamic effects, during coronary arterial surgery 53
 hemodynamic effects, in newborn piglet 633
 mechanism of action on striated muscle of rabbit 457
 myocardial ischemia during coronary artery occlusion with (abstract) S40
 myocardial metabolism during coronary arterial surgery 53
 naloxone and 330
 nicardipine and (abstract) S74
 oxygen consumption and (abstract) S107
 partial pressure effects on solubility in blood 672, 960
 pediatric, induction (letter) 1365
 pediatric, outpatient anesthesia 181
 pharmacokinetics (abstract) S84
 pharmacokinetics, comparative 575
 platelet aggregation effects of 1170
 seizures after 1235; (letter) 819
 thiopental and epinephrine-induced dysrhythmias with 437
- methoxyflurane
 cimetidine effect on 481
 pharmacokinetics, comparative 575
- Antacids, see Gastrointestinal tract**
- Antagonists, miscellaneous**
 physostigmine
 anesthesia reversal for intraoperative neurological testing 1059
 cerebrovascular and cerebral metabolic effects of 639
- Antagonists, narcotic**
 naloxone
 cardiovascular effects of fentanyl reversal (abstract) S99
 hypoxic depression of ganglionic transmission with 489
 inhalation anesthetics and 330
 morphine interactions with 615; (letter) 313, 1252
- Antagonists, neuromuscular relaxants**
 edrophonium
 atropine and (abstract) S96
 pharmacokinetics in elderly (abstract) S142
 refractive bradycardia and 1237
- Apnea, see Ventilation**
- Arrhythmias, see Heart**
- Aspiration, see**
 Gastrointestinal tract, stomach
 Lung
- Atracurium, see Neuromuscular relaxants**
- Barbiturates, see Hypnotics**
- Baroreflexes, see Reflexes**
- Benzodiazepines, see Hypnotics**
- Beta-adrenergic receptors, see**
 Sympathetic nervous system
- Biliary tract, see Liver**
- Binding, see Protein binding**
- Biotransformations, drug**
 cimetidine 481
 halothane 1257
 meperidine 536
- Blood patch, see Anesthetic techniques, epidural**
- Blood**
 anticoagulants, heparin 1201
 coagulation, heparin
 hemodynamic effects of 78
 protamine rate of administration and 377
 thrombocytopenia associated with 5
 coagulation, protamine
 administration via left atrium, right atrium, and peripheral vein compared (abstract) S27
 diabetes and 739
 hemodynamic effects of 78
 hypotension and (abstract) S68
 prostacyclin and thromboxane changes (abstract) S83
 pulmonary hypertension and (abstract) S86
 rate of administration, effects of 377
 ventricular function affected by 127
 coagulation, protein C deficiency and 982
 cold agglutination (letter) 1247
 platelets

Blood—*continued*platelets—*continued*

- halothane nucleotide depletion test 171
- isoflurane effects on 1170
- local anesthetic effect on (abstract) S63
- nitrous oxide effects on 1170
- slow channel calcium blocker effects on (abstract) S66

Book reviews

- 1985 Yearbook of Anesthesia, Mark H. Harris 709
- 1985 Yearbook of Critical Care Medicine, Morris Brown 430
- Acid-Base Regulation and Body Temperature, David R. Bevan 997
- Acute Pain, Robert G. Burney 214
- Acute Respiratory Failure, Robert R. Kirby 214
- Advances in Anesthesia (volume three), John R. Moyers 994
- Anaesthesia in the Elderly, Stanley Muravchick 993
- Anaesthetic Equipment: Physical Principles and Maintenance, Philip T. Conroi 1255
- Anesthesia (second edition), Paul Martin Kempen 994
- Anesthesia and Coronary Artery Surgery, F. G. Estafanous 993
- Anesthesia and Sedation in the Dental Office, Sanford L. Klein 1094
- Anesthesia for Ambulatory Surgery, Herbert D. Weintraub 997
- Anesthesia in Obstetrics: Maternal, Fetal, and Neonatal Aspects, Hilda Pedersen 1374
- Atlas of Regional Anesthesia, James C. Erikson III 550
- Basic Physics and Measurement in Anesthesia (second edition), Kevin K. Tremper and Steven J. Barker 1372
- Cardiac Catheterization and Angiography (third edition), William J. Greeley 1094
- Case Studies in Critical Care Medicine, John W. Hoyt 323
- Classical Anesthesia Files, Lee H. Cooperman 429
- Controlled hypotension in Neuroanaesthesia, Jane Matjasko 323
- Current European Anaesthesiology (volume 1), Alan W. Grogono 995
- Effects of Anesthesia, Lee H. Cooperman 323
- GASMAN—Understanding Anesthesia Uptake and Distribution, Barbara W. Brandom 107
- Guidelines in Clinical Anaesthesia, J. R. Marshall 996
- Handbook of Physiology, Section 3: The Respiratory System. Volume I. Circulation and Nonrespiratory

- Functions, Bryan E. Marshall and Horatio C. Wood 426
- Handbook of Regional Anesthesia, Stephen J. Prevoznik 106
- Head Injury and the Anaesthetist, Michael M. Todd 1095
- High-Frequency Ventilation in Intensive Care and during Surgery, E. Paul Didier 215
- Intensive Care Medicine, Donald C. Finlayson 1255
- International Anesthesiology Clinics, Eric B. Furman 709
- Invasive Procedures in Critical Care, Douglas B. Coursin 1372
- Isoflurane (Forane): A Compendium and Reference (second edition), Judith B. Dillman 1372
- Labat's Regional Anesthesia, Techniques and Clinical Applications, Andrea M. Baldeck 429
- Legal Issues in Transfusion Therapy: Managing Risks in a Changing Environment, William H. R. Dornette 1374
- Matters of Life and Death: Risks vs Benefits of Medical Care, William K. Hamilton 1096
- Molecular and Cellular Mechanisms for Anesthetics, Gerald A. Gronert 1371
- Monitoring in Anesthesia and Critical Care Medicine, Alan Jay Schwartz 428
- Muscle Relaxants: Basic and Clinical Aspects, Martin D. Sokoll 1095
- Perioperative Cardiac Dysrhythmias: Mechanisms, Recognition, Management, Carol L. Lake 106
- Precis D'Anesthésie Loco-Regionale, Helen R. Westman 107
- Primer of Water, Electrolyte and Acid-Base Syndromes, Perry G. Fine 1254
- Pulmonary Development, Transition from Intrauterine to Extrauterine Life, John G. Shutack 427
- Recent Advances in Anaesthesia and Analgesia, John A. Youngberg 324
- Regional Anesthesia and Clinical Applications, Eli M. Brown 216
- Spinal Injury (second edition), Robert W. McPherson 996
- Textbook of Pain, Michael J. Cousins 548
- The Heart: Physiology, Metabolism, Pharmacology, and Therapy, Carolyn J. Wilkinson 1253
- The Management of Postoperative Pain, Robert Friedman 996
- The Manual of Pediatric Anesthesia, Lawrence M. Borland 108
- The Origins of Anesthesia, John J. Leahy 323
- The Pharmacological Basis of Therapeutics (seventh edition), D. Ryan Cook 1253

The Pregnant Surgical Patient, A. Scott Wheeler 549

The Resident's Friend, Steven L. Shafer 216

Update in Intensive Care and Emergency Medicine, John W. Hoyt 322

Brachial plexus, see Anesthetic techniques, regional

Brain

blood flow

- benzodiazepine antagonist effect on 639
 - chemoreflex hypocapnia effect on (abstract) S37
 - halothane effects after brain injury (abstract) S133
 - hemodilutional resuscitation and (abstract) S121
 - isoflurane effect on 565
 - isoflurane effect on, after brain injury (abstract) S133
 - isoflurane effect on, hypotension and 660
 - midazolam effects on 639, 729
 - nimodipine and (abstract) S98
 - phenobarbital and (abstract) S115
 - physostigmine effect on 639
 - thromboxane synthetase inhibitor and (abstract) S122
- blood-brain barrier
- anesthetic management during therapeutic disruption of 188
- cerebrospinal fluid pressure
- nicardipine effects on 507
- cholinergic dysfunction and anesthetic state (letter) 210
- coma
- barbiturate-induced 1196
 - drug-induced, reversal of 1222
- coronary vein thrombosis during pregnancy 1007
- electroconvulsions 1345
- electroencephalogram
- patterns during pediatric cardiac operations with isoflurane 525
- endorphins, 330
- evoked potentials
- anterior cervical spinal fusion effect on 96
 - cardiovascular anesthesia effect on (abstract) S85, S141
 - fentanyl effect on (abstract) S136
 - hypocapnia effect on 240; (abstract) S134
 - hypothermia effect on 475
 - intracranial gas effects during craniectomy 203
 - lidocaine effect on (abstract) S16
 - nalbuphine effect on (abstract) S51
 - sufentanil effect on (abstract) S81
 - thiopental effect on (abstract) S80
- intracranial pressure

- atracurium effects on 381
nicardipine effects on 507
- Bupivacaine**, see Anesthetics, local
- Butorphanol**, see Analgesics
- Caffeine**, see Pharmacology
- Calcium**, see Ions
- Cannulation**, see Veins
- Capnograph**, see Measurement techniques
- Carbon dioxide**
apnea and increased measurements of (abstract) S153
hypercarbia
ventilatory and circulatory responses to 9
hypocapnia
isoflurane-induced hypotension and 660
median nerve somatosensory responses and 240
intraoperative arterial vs peak end tidal partial pressure of (abstract) S41
laser for debulking of laryngeal tumor 1225
single breath tests 645
- Carbon monoxide** see Gases, non-anesthetic
- Cardiopulmonary bypass**, see Anesthesia, cardiovascular
Surgery, cardiovascular
- Cardiovascular system**, see Anesthesia, cardiovascular
Heart
Individual organs
Reflexes
Surgery, cardiovascular
Veins
- Catecholamines**, see Sympathetic nervous system
- Catheters**, see Equipment
- Cerebral blood flow**, see Brain, blood flow
- Children**, see Anesthesia, pediatric
- Chloral hydrate**, see Hypnotics
- 2-Chloroprocaine**, see Anesthetics, local
- Cigarette smoke**, see Lung
- Cimetidine**, see Gastrointestinal tract, stomach
- Circuits, anesthetic**, see Equipment
- Clonidine**, see Sympathetic nervous system, alpha agonists
- Coagulation**, see Blood
- Cocaine**, see Anesthetics, local
- Complications**
acquired immune deficiency syndrome 1054
bronchospasm 417
burns 1340
convulsions
fentanyl-etomidate anesthesia and 979
isoflurane anesthesia and 1235
local anesthetics and 1063
cystic fibrosis 1357
diabetes 739, 1237
eosinophilic myositis 903
epilepsy
etomidate effect on EEG of 1004
esophageal intubation 886
headache
pediatric oncology patients with (abstract) S21
postdural puncture 1242
postdural puncture, caffeine for, (letter) 316
postdural puncture, epidural blood patch for 895
Marfan's syndrome 411
mastocytosis
anesthetic management of (abstract) S117
morbidity
anesthetic (abstract) S42
mortality (letter) 422
myotonic dystrophy 687, 1066
obesity
Pickwickian syndrome management of 985
preoxygenation (abstract) S106
ranitidine effects on gastric contents 195
ventilator settings to reduce hypocarbia (abstract) S53
pneumocephalus, 65
protein C deficiency 982
shivering
elderly patients and (abstract) S108
epidural anesthesia and (abstract) S164
intravenous fluid temperature and 496
subarachnoid hematoma 1201
torticollis 1077
Tourette syndrome, 200
- Contractility**, see Heart
Muscle, skeletal
- Convulsions**, see Complications
- Coronary**, see Heart
- Curare**, see Neuromuscular relaxants, d-tubocurarine
- Cushing, Harvey**, see History
- d-Tubocurarine**, see Neuromuscular relaxants
- Dantrolene**, see Heart
Neuromuscular relaxants
- Dezocine**, see Analgesics
- Diazepam**, see Anesthetics, intravenous
Hypnotics, benzodiazepines
- Diltiazem**, see Heart, myocardial function
Pharmacology
- Dinoprost**, see Pharmacology
- Doppler ultrasound**, see Measurement techniques
Monitoring
- Down's syndrome**, see Complications
- Echocardiography**, see Heart
Measurement techniques
- Eclampsia** see Anesthesia, obstetric
- Edrophonium** see Antagonists, neuromuscular relaxants
- Electrocardiography**, see Heart
- Electroconvulsions**, see Brain
- Electroencephalogram**, see Brain
- Electromyogram**, see Measurement techniques
Muscle, skeletal
- Embolism**
air
Bunegin-Albin CVP catheter for resuscitation (abstract) S7
junctional rhythm mimicking of 1083
test for adequate Doppler placement (abstract) S135
venous, in total hip arthroplasty (abstract) S150
amniotic fluid
ventricular tachycardia and hypotension with 533
fat
femoral neck fractures and 892
- Endobronchial techniques** see Anesthetic techniques
- Endorphins**, see Brain
- Enflurane**, see Anesthetics, volatile
- Eosinophilic myositis**, see Complications
- Epidural technique**, see Anesthetic techniques
- Epilepsy**, see Complications
- Epinephrine**, see Heart, arrhythmias
Sympathetic nervous system
- Equipment**
ampules 1361
breathing tubes (letter) 1365
catheters
arterial, sterility of 1218; (abstract) S109
Racz catheter safety (letter) 821
carbon dioxide laser for debulking of laryngeal tumor 1225
circuits, nonbreathing (letter) 1248
elbow adapters (letter) 824
endobronchial tubes
Robertshaw-type, hazardous placement of 100
endotracheal tubes
breathing through 853
foam cuff T-piece system 1359
leak pressure and tracheal lumen size in swine 667
leaks around cuffs of 777
RAE and CAT tubes and pressure loss (abstract) S11
tube size correlation to sore throat after anesthesia (abstract) S155
exhaust systems (letter) 102
fiberoptic bronchoscope 389

Equipment—*continued*

- flowmeters (letter) 211
- humidifiers (letter) 1247
- infusion systems, "piggyback" (letter) 209
- stethoscopes
 - esophageal (letter) 319
- syringes
 - labelling of, confusion in (letter) 104
- tourniquet
 - pain of 1175, 1181
 - systemic responses to release in children 865
- vaporizers
 - alarms for (letter) 1364
 - nitrous oxide solubility in volatile anesthetics causing aberrancy of 88
 - output increase with nitrous oxide elimination (letter) 823
- ventilators
 - fresh gas flow change effect on tidal volume (abstract) S4

Esmolol, see

- Heart
- Sympathetic nervous system, pharmacology

Esophagus, see Gastrointestinal tract

Etidocaine, see Anesthetics, local

Etomidate, see Anesthetics, intravenous

Evoked potentials, see

- Brain
- Monitoring

Eye

- intraocular pressure
 - atracurium effect on 877
 - vecuronium effect on 877
- ophthalmic ointments (letter) 1091

Fasting, see Gastrointestinal tract, stomach

Fentanyl, see

- Analgesics
- Anesthetics, intravenous

Fibrillation, see Heart, arrhythmias

Flowmeters, see Equipment

Fluorocarbons, see Pharmacology

Fontan procedure, see

- Anesthesia, cardiovascular
- Surgery, cardiovascular

Gases, non-anesthetic

- carbon monoxide
 - noninvasive oxygen monitoring affected by (abstract) S12

Gastrointestinal tract

- antacids
 - metoclopramide effects on gastric contents in morbidly obese patients 195
 - ranitidine, gastric contents in morbidly obese patients affected by 195
 - ranitidine, in children (abstract) S170
- esophagus
 - intubation through 886
 - prestenotic dilation of 901

histamine antagonists

- midazolam interactions with 176
- stomach
 - barotrauma (letter) 540
 - cimetidine (abstract) S147
 - cimetidine, local anesthetic CNS toxicity and 840
 - cimetidine, midazolam interactions with 176
 - pH and aspiration risk factors (letter) 210
 - preoperative emptying of 1112
 - ranitidine, local anesthetic CNS toxicity and 840
 - ranitidine, midazolam interactions with 176
 - sodium citrate effects on (abstract) S147

Genetic factors

- halothane sensitivity 1143

Geriatric, see Anesthesia, geriatric

Griffith, H. R., see

- History
- Obituary

Halothane, see Anesthetics, volatile

Headache, see Complications

Hearing,

- deafness
 - spinal anesthesia treated with epidural blood patch as factor in 312

Heart

- arrhythmias
 - air embolism and 1083
 - amiodarone and 414; (abstract) S49
 - chloral hydrate and 691
 - epinephrine-induced 437
 - lidocaine effect on ventricular defibrillation 337
 - local anesthetics and 133
 - mitral valve prolapse and 975
 - terbutaline-induced 417
 - thiopental-induced 437
 - verapamil treatment (letter) 102
- bupivacaine toxicity 911
- cardiac output
 - alfentanil with halothane anesthesia and 765
- contractility
 - halothane and verapamil interaction 463
 - intraoperative determination of (abstract) S72
 - local anesthetic effects on 1263
- coronary blood flow 294
 - diltiazem effects during enflurane anesthesia 918
 - diltiazem effects during isoflurane anesthesia 81
- coronary circulation
 - anatomy 294
 - myocardial oxygenation in coronary artery disease 395
- dantrolene
 - atrioventricular conduction and 5

echocardiography

- intraoperative left ventricular wall motion (abstract) S1
- electrocardiography
 - lead systems compared (abstract) S65
 - thiopental and epinephrine-induced dysrhythmias 437
- esmolol
 - continuous infusion during cardiac operation (abstract) S70
- hypoplastic left heart syndrome
 - fentanyl anesthesia for surgical repair of 127
- lidocaine toxicity 911
- mitral valve prolapse 975
- myocardial function
 - amrinone effects 849
 - dantrolene effects 252
 - diltiazem effects 1099
 - diltiazem effects, during enflurane anesthesia 918
 - diltiazem effects, during isoflurane anesthesia 81
 - halothane effects 431
 - isoflurane effects 633
 - local anesthetic effects 551
 - nitrous oxide effects 431
 - protamine effects 1271
 - recovery from general anesthesia and 593
 - verapamil effects 252, 1099
- myocardial infarction
 - percutaneous transluminal coronary angioplasty for 815
 - reinfarction after anesthesia (abstract) S95
 - thoracic epidural anesthesia effects on 711
- myocardial ischemia
 - during induction 617
 - spinal anesthesia and reversal of 908
- nifedipine
 - hypotension and endocrine response (abstract) S151
- oxygenation
 - hemodilution effects in dogs (abstract) S38
 - myocardial, in coronary artery disease 395
- pacemakers
 - artificial (abstract) S32
 - postoperative termination of atrial flutter in (abstract) S32
- prolonged QT interval syndromes (letter) 212
- verapamil
 - AV conduction effects 252
 - halothane effects 463
 - intractable reperfusion ventricular tachycardia/fibrillation treatment with (letter) 102

Henry's Law see

- Physics
- Solubility

Heparin, see

- Blood, anticoagulants
- Blood, coagulation

Hepatotoxicity, see Liver**Heroin**, see Analgesics**Herpes**, see Infection**High frequency ventilation**, see
Ventilation**History**

- Cushing, Harvey 288; (letter) 1249
- Griffith, Harold 1051

Hormones

- thyrotropin-releasing hormone
cardiorespiratory potency effects of
(abstract) S132
- cortisol
isoflurane effect on 1117
- progesterone
plasma and CSF concentrations
during pregnancy 950
- prostaglandins
leukotrienes in pulmonary edema
fluid 306

Hydromorphone, see Analgesics**Hypercarbia**, see Carbon dioxide**Hyperpyrexia**, see Hyperthermia,
malignant**Hyperthermia**

- malignant
masseter muscle rigidity and 161
platelet-halothane nucleotide
depletion test of 171
sudden infant death syndrome and
(letter) 209
tourniquet-twitch test for 1047
vecuronium and (letter) 212

Hypnotics

- barbiturates
brain injury from 1196
pentobarbital, antinociceptive
interaction with morphine 601
thiopental, psychomotor skills and
amnesia after induction 933
- benzodiazepines
cerebrovascular and cerebral
metabolic effects of 639
diazepam, alfentanil induction and 71
diazepam, bupivacaine kinetics and
151
lorazepam, pretreatment for
sufentanil anesthesia 703
midazolam, aminophylline
antagonism of (letter) 540
midazolam, cerebral blood flow
effects of 639, 729
midazolam, cerebral metabolic effects
of 639
midazolam, cimetidine interactions
with 176
midazolam, intravenous agent in
elderly 15; (letter) 1089
midazolam, meperidine
postoperatively and (abstract) S46
midazolam, nitrous oxide interaction
with 729

- midazolam, oxygen consumption
effects of 729
- midazolam, plasma levels in pregnant
vs nonpregnant women (abstract)
S167
- midazolam, psychomotor skills and
amnesia after induction 933
- midazolam, ranitidine interactions
with 176
- chloral hydrate
arrhythmias from 691

Hypocapnia, see Carbon dioxide**Hypoplastic left heart syndrome**, see
Heart**Hypotension**, see Anesthetic techniques,
hypotensive**Hypothermia**

- evoked potentials and 475
- postanesthetic (letter) 825

Hypoxia

- metabolism during 1130
- naloxone effects 489
- nitrous oxide effects 62
- postanesthetic pediatric 267

Induction

- anesthesia
alfentanil, diazepam and 71
alfentanil, thiopental compared to
(abstract) S146
cardiovascular responses 1037
device for smoothing pediatric
induction (letter) 1366
diprivan, thiopental compared to
(abstract) S162
fentanyl, cardiovascular responses to
91
midazolam, as intravenous agent in
elderly 15; (letter) 1089
myocardial ischemia prevention 617
propofol, methohexital compared to
(abstract) S2
propofol, thiopental compared to
(abstract) S2, S89
rapid sequence 503
sulfentanil-diazepam and
fentanyl-diazepam compared
(abstract) S82
vecuronium priming for (letter) 1367

Infection

- acquired immune deficiency syndrome
anesthesia personnel and (abstract)
S126
operative procedures and (abstract)
S127
overview 1054
spinal and epidural anesthesia with
(letter) 1090
catheter-induced 1218
herpes zoster, reflex sympathetic
dystrophy and 309

Infusion equipment, see Equipment**Interactions, drug**

- calcium channel blockers and
anesthetics 463
- fentanyl and thiopental 1149

- lorazepam and sufentanil 703
- midazolam and histamine antagonists
176
- midazolam and nitrous oxide 729
- morphine and halothane (letter) 319
- morphine and naloxone (letter) 1252
- morphine and thiopental 1149
- nitroglycerine and neuromuscular
relaxants 156
- verapamil and halothane 463

Intercostal block, see Anesthetic
techniques, regional**Intracranial pressure**, see Brain**Intraocular pressure**, see Eye**Intravenous anesthesia**, see

- Anesthetic techniques
- Anesthetics, intravenous

Intubation, tracheal

- aspiration due to leaks around cuffs of
tubes in 777
- atracurium with thiopental for 1295
- blind (letter) 825
- breathing through tubes in 853
- cardiovascular responses to 389
- detection techniques 886
- esmolol and fentanyl compared for
(abstract) S45
- lidocaine absorption with 389
- myocardial ischemia associated with
617
- tranillumination of trachea for (letter)
542
- transtracheal jet ventilation during
(letter) 1091
- tube leak pressure and tracheal size in
swine 667

Ions

- calcium
diltiazem effects during isoflurane
anesthesia 81
mechanism of action of volatile
anesthetics on muscle 457
- magnesium
succinylcholine and 373
- potassium
hyperkalemia in patient with cold
agglutinins (letter) 1247
succinylcholine and 373

Isoflurane, see Anesthetics, volatile**Jugular veins**, see Veins**Ketamine**, see Anesthetics, intravenous**Ketanserin**, see Serotonin**Kidney**

- lidocaine clearance from 943
- renal failure
atracurium pharmacodynamics with
743
open heart surgery, occurrence after
(abstract) S57

Labor, see Anesthesia, obstetric**Laser**, see Carbon dioxide**Leukotrienes**, see Hormones,
prostaglandins**Lidocaine**, see Anesthetics, local**Lithotripsy**, see Surgery, urologic

Liver

- biliary tract
 - alfentanil and fentanyl effects on pressure of 370
- blood flow
 - controlled hypotension and (letter) 423
- hepatotoxicity
 - cimetidine-induced 481
 - enflurane-induced 21; (letter) 545
 - genetic predisposition to 1143
 - halothane-induced (editorial) 831
 - isoflurane-induced (letter) 545
- lidocaine clearance from 943
- microsomes
 - halothane hepatotoxicity and (editorial) 831
 - halothane reductive defluorination and 835
- transplantation
 - perioperative neurotensin and vasoactive intestinal peptide levels (abstract) S79

Local anesthetics, see Anesthetics, local

Lorazepam, see Hypnotics, benzodiazepines

Lung

- edema
 - early detection in swine (abstract) S118
 - leukotrienes in fluid after cardiopulmonary bypass 306
 - oleic acid-induced 925
- aspiration
 - myotonia dystrophy and 1066
 - tracheal tube cuff leaks causing 777
- blood flow
 - atropine and glycopyrrolate effects on 1285
 - nitrous oxide effects on 62
- cigarette smoke
 - halothane anesthesia affected by 37
- gas exchange in children 645
- surfactant films of 1275
- trachea
 - anesthesia (letter) 315
 - tumor of, anesthetic management of 1227
- ventilatory mechanics, anesthetic implications 1

Magnesium, see Ions

Marfan's syndrome, see Complications

Mastocytosis, see Complications

Measurement techniques

- capnograph (letter) 990
- Doppler ultrasonography
 - cardiac output monitoring via 1013
- echocardiography
 - intraoperative left ventricular wall motion (abstract) S1
- electromyography
 - train-of-four responses during neuromuscular blockade 771
- esophageal stethoscopes for anesthetic depth (letter) 319

- neuromuscular blockade (letter) 425
- nuclear magnetic resonance
 - anesthetics and sedatives affecting (abstract) S56
 - remote control anesthesia during (abstract) S88
- oximetry 1333
 - monitoring probes for (letter) 826
 - nail polish effects on (letter) 824
 - transcutaneous measurements vs 805
- oxygenation 805
- sensory blockade 843

Memory

- amnesia
 - midazolam or thiopental induction and 933
- anesthesia and (letter) 988
- intraoperative, evidence of partial recall (abstract) S154
- selective (letter) 988

Meperidine, see Analgesics

Metabolism

- acetaldehyde syndrome 1300
- atracurium (letter) 1368
- diabetes and 1237
- high energy phosphate 1130
- oxygen consumption with nitrous oxide 355

Methohexital, see Anesthetics, intravenous

Methoxyflurane, see Anesthetics, volatile

Metoclopramide, see Gastrointestinal tract, antacids

Metocurine, see Neuromuscular relaxants

Midazolam, see

- Anesthetics, intravenous
- Hypnotics, benzodiazepines
- Induction, anesthesia

Monitoring

- cardiorespiratory monitoring during radiation therapy 529
- Doppler ultrasound of cardiac output 1013
- evoked responses
 - cervical spinal cord function assessment via 96
 - intracranial gas effects during craniectomy 203
 - pulse rate changes during epidural anesthetic test doses (letter) 1089
 - ulnar nerve block quantification via 843
- neuromuscular function 771
 - electromyograph vs twitch tension (abstract) S47
- oximetry 1333
- oxygen
 - inspired concentrations (letter) 1248
 - saturation (letter) 213
 - saturation, pediatric anesthesia and 267
 - venous, as indicator of oxygenation during thoracic surgery (abstract) S34
- plethysmograph 1333

ventilation

- patient weaning from mechanical respiratory support with (abstract) S34

Morbidity, see Complications

Morphine, see Analgesics

Muscle, skeletal

- contractility
 - isoflurane and halothane effects on 457

Myotonic dystrophy, see Complications

Nalbuphine, see Analgesics

Naloxone, see Antagonists, narcotic

Narcotics, see

- Analgesics
- Anesthetics, intravenous

Neonates, see

- Anesthesia, obstetric
- Anesthesia, pediatric

Neuromuscular relaxants

- atracurium
 - cerebral perfusion pressure effects of 381
 - endotracheal intubation in children with (abstract) S103
 - hemodynamic effects in cardiac surgical patients (abstract) S54
 - histamine release in children (abstract) S61
 - in vitro degradation of (letter) 543
 - inactivation of (letter) 1368
 - intracranial pressure effects of 381
 - intraocular pressure effects of 877
 - intubation with vecuronium and (abstract) S87
 - ketamine continuous infusion with 860
 - neuromuscular function recovery after 1042
 - neuromuscular transmission effect of 345
 - pharmacokinetics during isoflurane anesthesia 743
 - pharmacology of (abstract) S137
 - pheochromocytoma and (letter) 211
 - priming dose of (abstract) S149
 - resistance to (letter) 820
 - succinylcholine compared to (abstract) S97
 - thiopental and 1295
 - torticollis diagnosis and treatment with 1077
 - toxicity of 1107
 - train-of-four response measurements 771
 - cost of (letter) 315, 422
- d*-tubocurarine
 - diaphragm sensitivity after limb immobilization 493
- dantrolene
 - atrioventricular conduction and cardiovascular effects of 252
 - hyperkalemia and (abstract) S131
 - measurement of response, randomized

- study of controlled hypertensives (abstract) S48
- metocurine
- administration of combined bolus and infusion (abstract) S9**
 - cardiovascular effects of 1340
 - neuromuscular responses to 1340
 - pharmacokinetics and pharmacodynamics of (abstract) S138
 - toxicity of 1107
- pancuronium
 - beta-blocker interactions with (abstract) S73
 - cardiovascular effects of 1340
 - neuromuscular blockade reversal and (abstract) S59
 - neuromuscular responses to 1340
 - nitroglycerin potentiation of 156
 - pharmacokinetics and pharmacodynamics of 233, 1319
 - resistance to (letter) 539
 - succinylcholine compared to (abstract) S97
 - vecuronium compared to 233
- pediatric 1208
- succinylcholine
 - beta-blockade and potassium release (abstract) S60
 - heart rate and rhythm effects of 1329
 - magnesium sulfate pretreatment 373
 - masseter muscle rigidity and 161
 - masseter muscle spasm and (letter) 1245
 - myalgias and (abstract) S148
 - myoglobinemia in children under isoflurane anesthesia and (abstract) S69
 - pancuronium compared to (abstract) S97
 - potassium levels in brain tumor patients and (abstract) S100
 - train-of-four response measurements 771
 - vecuronium compared to (abstract) S97
- vecuronium
 - cardiovascular effects on digitalized dogs (abstract) S23
 - closed-loop feedback control (abstract) S45
 - continuous infusion of (abstract) S25
 - dose-response relationship with phenytoin (abstract) S116
 - hemodynamic effects in cardiac surgical patients (abstract) S54
 - histamine release in children (abstract) S61
 - intracranial pressure and (abstract) S101
 - intraocular pressure effects of 877; (abstract) S10
 - intubation with atracurium and (abstract) S87
- malignant hyperthermia and (letter) 212
- nitroglycerin potentiation of 156
- pancuronium compared to 233
- pharmacokinetics and pharmacodynamics of 233, 1319
- priming effect in children (abstract) S160
- rapid sequence induction with 503; (letter) 1367
- succinylcholine compared to (abstract) S97
- train-of-four response measurements 771
- urinary excretion with normal renal function vs renal failure 245
- Neurosurgery, see**
 - Anesthesia, neurologic
 - Surgery, neurologic
- Nicardipine, see Pharmacology**
- Nifedipine, see**
 - Heart
 - Pharmacology
- Nitroglycerine, see Pharmacology**
- Nitroprusside, see Anesthetic techniques, hypotensive**
- Nitrous oxide, see Anesthetics, gases**
- Norepinephrine, see Sympathetic nervous system**
- Normeperidine, see Analgesics, meperidine**
- Nuclear magnetic resonance, see Measurement techniques**
- Obesity, see Complications**
- Obituary**
 - Griffith, Harold 1051
- Obstetrics, see Anesthesia, obstetrics**
- Opioids, see Analgesics**
- Organizations**
 - Nuffield Department of Anaesthetics, University of Oxford (letter) 211
- Orthopedics, see Surgery**
- Outpatient anesthesia, see Anesthesia, outpatient**
- Oximetry, see Measurement techniques**
- Oxygen**
 - halothane defluorination and 835
 - inspired concentrations (letter) 1248
 - nitrous oxide effect on mitochondrial consumption of 355
 - saturation
 - pediatric anesthesia and 267
 - stabilization of monitor probe in infants and children (letter) 213
 - transit from or to recovery rooms affecting (abstract) S62
 - transcutaneous measurements of 805
- Pacemakers, artificial, see Heart**
- Pain**
 - cervical
 - epidural anesthetic management of 938
 - chronic
 - epidural morphine for 531
 - implantable intraspinal narcotic delivery systems for 883
 - low back
 - cocaine or lidocaine block of sphenopalatine ganglion for 700; (abstract) S17
 - perception of, dual system hypothesis for (letter) 313
 - post-thoracotomy
 - intrathecal morphine for 873
 - postoperative
 - butorphanol for 283
 - dezocine for 283
 - diacetylmorphine for 1290
 - ketamine for, epidural (letter) 989
 - lumbar epidural anesthesia for 1069
 - morphine for, epidural 165, 1033
 - anorectal surgery and 499
 - oral controlled release vs 385
 - tourniquet 1175, 1181
 - vascular responses to 601
- Pancuronium, see Neuromuscular relaxants**
- Parasympathetic nervous system**
 - atropine effects 1285
 - glycopyrrolate effects 1285
- Pediatrics, see Anesthesia, pediatric**
- PEEP, see Ventilation, positive end-expiratory pressure**
- Pentobarbital, see Hypnotics, barbiturates**
- Peridural technique, see Anesthetic techniques, epidural**
- pH, see Gastrointestinal tract, stomach**
- Pharmacokinetics**
 - alfentanil 999, 1021, 1155
 - atracurium 743
 - bupivacaine 151, 1281
 - fentanyl in neonates 227; (letter) 1369
 - heroin 718
 - inhalation anesthetics
 - comparative 575
 - duration effect on (abstract) S26
 - lidocaine 943, 1281
 - pediatric, 279
 - preeclampsia and 120
 - morphine 718
 - pancuronium 233, 1319
 - protein binding 786
 - sufentanil (abstract) S64
 - vecuronium 233, 245, 1319
- Pharmacology**
 - aminophylline
 - midazolam antagonism and (letter) 540
 - amrinone
 - cardiovascular effects during enflurane anesthesia 849
 - cardiovascular effects in dogs (abstract) S91
 - caffeine
 - postdural puncture headache treatment (letter) 316
 - calcium channel blockers 507
 - anesthetic metabolism and toxicity effects of 481
 - beta blockers combined with 905

Pharmacology—continued

- dantrolene
 - atrioventricular conduction and cardiovascular effects of 252
- diltiazem 81, 918, 1099
- dinoprost (letter) 1248
- fluorocarbons 734
- nicardipine 507, 706
- nifedipine (abstract) S24
- nitroglycerin
 - myocardial ischemia prevention and 617
- pancuronium- and vecuronium-induced neuromuscular blockade with 156
- propranolol 1099
- terbutaline 417
- theophylline (letter) 423
- verapamil 1099
 - atrioventricular conduction and cardiovascular effects of 252
 - cardiac electrophysiology in rabbit affected by (abstract) S22
 - intractable reperfusion ventricular tachycardia/fibrillation treatment with (letter) 102
- Phenylephrine**, see Sympathetic nervous system, alpha agonists
- Pheochromocytoma**, see Surgery
- Physics**
 - Henry's law 960
- Physostigmine**, see Antagonists, miscellaneous
- Pituitary**, see Brain
- Platelets**, see Blood
- Pneumocephalus**, see Complications
- Position**
 - axillary artery compression and (letter) 318
 - pneumocephalus correlation to 65
- Potassium**, see Ions
- Preeclampsia**, see Anesthesia, obstetric
- Pregnancy**, see Anesthesia, obstetric
- Premedication**
 - arterial blood gases in cardiac surgical patients and (abstract) S110
 - pharmacologic and clinical aspects of 963
 - stress-related increase in plasma beta-endorphin levels and (abstract) S123
- Procaine**, see Anesthetics, local
- Progesterone**, see Hormones
- Propofol**, see
 - Anesthesia, intravenous
 - Induction, anesthesia
- Protamine**, see Blood, coagulation
- Protein binding**
 - bupivacaine (letter) 314
 - diazepam (letter) 314
 - drug, plasma 786
- Psychologic response**
 - halothane exposure effect on 653
 - postanesthetic 955; (letter) 543
- Publications**
 - currentness evaluation of (letter) 422

Ranitidine, see

- Gastrointestinal tract, antacids
- Gastrointestinal tract, stomach
- Recall**, see Memory
- Recovery**
 - myocardial function 593
 - psychomotor tests 955; (letter) 543
- Reflexes**
 - baroreceptors
 - diazepam and midazolam effects on 113
- Relaxants**, see Neuromuscular relaxants
- Respiration**, see
 - Metabolism, oxygen consumption
 - Ventilation
- Ritodrine**, see
 - Anesthesia, obstetric
- Scavengers**, see Equipment, exhaust systems
- Seizures**, see
 - Complications, convulsions
 - Complications, epilepsy
- Serotonin**
 - cardinoid tumors and 809
 - ketanserin and 809
 - sufentanil-reduced MAC and (abstract) S5
- Shivering**, see Complications
- Solubility**
 - halothane, partial pressure effects on 960
 - Henry's law 672
 - isoflurane, partial pressure effects on 960
- Somatosensory evoked responses**, see
 - Brain, evoked potentials
 - Monitoring, evoked potentials
- Spinal anesthesia**, see Anesthetic techniques
- Spinal cord**
 - blood flow, clonidine effects on 1312
 - narcotic effects on 145
- Stethoscope**, see Equipment
- Stomach**, see Gastrointestinal tract
- Succinylcholine**, see Neuromuscular relaxants
- Sufentanil**, see
 - Analgesics
 - Anesthetics, intravenous
- Surgery**
 - cardiovascular
 - aortocoronary bypass, esmolol effects on fentanyl-pancuronium anesthesia for 451
 - CABG surgery, fentanyl anesthesia with lidocaine for 511
 - cardiopulmonary bypass, leukotrienes in pulmonary edema fluid after 306
 - cardiopulmonary bypass, thiopental for (abstract) S111
 - coronary arterial surgery, isoflurane for 53
 - fentanyl-enflurane anesthesia for 46
 - Fontan procedure 516
 - opiate anesthesia for 259

- percutaneous transluminal coronary angioplasty 815
- maxillofacial
 - controlled hypotension for 683
- neurologic
 - blood-brain barrier disruption during 188
 - pneumocephalus incidence during 65
 - reversible loss of somatosensory evoked potentials during 96
- orthopedic
 - femoral neck fractures in elderly 892
 - general vs regional techniques for knee arthroscopy 185
 - morphine for postoperative pain relief 165
- pheochromocytoma 706; (letter) 211
- urologic
 - lithotripsy for 1231
- vascular
 - morphine for postoperative pain relief 165
- Sympathetic nervous system**
 - alpha agonists
 - clonidine, potentiation of nitroprusside with 469
 - clonidine, regional and central hemodynamic effects of 1312
 - clonidine, spinal cord blood flow effect of 1312
 - clonidine, subarachnoid toxicity of 1303
 - guanfacine, subarachnoid toxicity of 1303
 - phenylephrine, isoflurane anesthesia and (abstract) S20
 - phenylephrine, prolongation of lidocaine spinal anesthesia 781
 - beta-adrenergic blockage
 - catecholamine and 1099
 - propranolol and 1099
 - catecholamines
 - diazepam and midazolam effects on 113
 - epinephrine
 - diazepam and midazolam effects on 113
 - norepinephrine
 - diazepam and midazolam effects on 113
 - halothane effect on saphenous vein uptake of 360
 - nitrous oxide effect on 551
 - pharmacology
 - esmolol, fentanyl-pancuronium anesthesia and 451
 - vasopressors, venous return during spinal anesthesia and 612
 - reflex sympathetic dystrophy 309
- Syringes**, see Equipment
- Temperature**
 - blood gas tensions corrected by (letter) 420
 - intravenous fluid 496, 693
- Terbutaline**, see Pharmacology

- Tetracaine**, see Anesthetics, local
Theophylline, see Pharmacology,
aminophylline
Theories of anesthetic action
endorphins 330
Thiopental, see Anesthetics, intravenous
Thyrotropin-releasing hormone, see
Hormones
Topical anesthesia, see
Anesthetic techniques
Anesthetics, local
Torticollis, see Complications
Tourette syndrome, see Complications
Tourniquet, see
Equipment
Pain
Toxicity
atracurium 1107
bupivacaine 341, 1263
halothane 653, 1257
lidocaine 1263
local anesthetic 133, 444, 840, 1029, 1063
metocurine 1107
Trace concentrations, see
Anesthetics, gases
Anesthetics, volatile
Equipment, scavenging
Transplantation, see Individual organs
Tubes, endotracheal, see Equipment,
endotracheal tubes
Urology, see Surgery
Uterus, see Anesthesia, obstetric
Vaporizers, see Equipment
Vasopressors, see Sympathetic nervous
system, pharmacology
Vecuronium, see Neuromuscular
relaxants
Veins
jugular, cannulation of (letter) 419, 901
Ventilation
anesthetics, effects of
active inspiratory impedance and load
compensation 1
duration of anesthesia as factor 1
apnea and, sleep 1222
breathing through endotracheal tubes
for 853
carbon dioxide response 9
cardiac function, mode of ventilation
and (abstract) S18
constant flow 1161
dead space, tidal volume and
respiratory rate (abstract) S114
high frequency
acute respiratory failure and 1135
extracorporeal shock wave lithotripsy
and 1231
gas entrainment factors (abstract) S15
ventricular function and 679
jet
oxygen and halothane entrainment
during 191
transtracheal (letter) 1091
patient weaning from mechanical
respiratory support (abstract) S29
pediatric
gas exchange during 645
positive end-expiratory pressure
acute respiratory failure and 1135
oleic acid-induced pulmonary edema
and 925
Ventilators, see Equipment
Verapamil, see
Heart
Pharmacology

IARS MEMBERSHIP

FOR YOUR IN-TRAINING AND CONTINUING MEDICAL EDUCATION

The International Anesthesia Research Society is a non-profit, scientific and educational corporation of the State of Ohio, founded in 1922 "to foster progress and research in anesthesia." To this end the Society

Publishes the oldest journal in the specialty, *Anesthesia and Analgesia*

Sponsors an annual scientific meeting (Congress) which is held in March each year

Funds anesthesia-related research through the IARS B.B. Sankey Anesthesia Advancement Award

Membership in the IARS is voluntary; it is also separate and distinct from membership in any other local, state, regional or national anesthesia organization or association. Membership is open to individuals who qualify in the various categories shown below; who complete the appropriate application and submit it to the IARS Cleveland office with the applicable dues. All memberships include a subscription to *Anesthesia and Analgesia*. Members and Associate Members are entitled to a reduced registration fee at the IARS annual meeting; Educational Members pay no registration fee.

. . . . MEMBERSHIP CATEGORIES

MEMBERSHIP: Open to individuals with doctorate degrees, who are licensed to practice in the medical, osteopathic, dental or veterinary medicine fields (i.e., MD, MB, DO, DDS, DMD, DVM); and to individuals with doctorate degrees in any scientific discipline (PhD), who are engaged in academic, private or commercial research.

ASSOCIATE MEMBERSHIP: Open to individuals in the allied health professions, duly certified by their professional accrediting organization as nurse anesthetists (CRNA); respiratory therapists or technicians (RRT or CRTT); physician/anesthesia assistants (PA/MMS); and other allied health professionals in anesthesia-related practice.

Annual Dues for Members and Associate Members: \$50.00 U.S.; \$61.00 foreign.

These memberships are entered on a calendar year basis only.

EDUCATIONAL MEMBERSHIP: Open (with certification by program director) to doctors (interns/residents) enrolled in anesthesiology training programs; nurses enrolled in nurse anesthesia schools; students enrolled in programs leading to certification as physician assistants, respiratory therapists or technicians

Annual Dues for Educational Members: One-half of member rate. These memberships are entered in January or July for 2, 3, or 4 year periods. Applications, certified by program directors, must accompany check to cover full membership period.

International Anesthesia Research Society
3645 Warrensville Center Road, Cleveland, Ohio 44122, USA

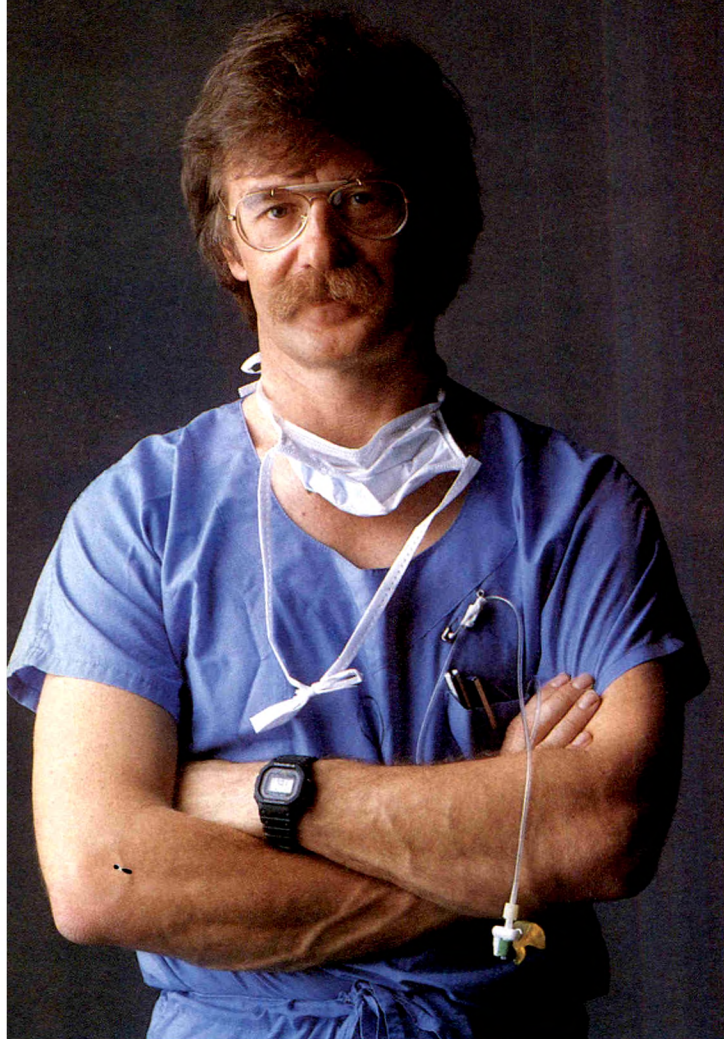
Please send me _____ application(s) for: Membership (_____)
Associate Membership (_____)
Educational Membership (_____)

Please print clearly: _____
Name and Degree (MD, DO, CRNA, RN, RRT, etc.)

Street Address

City, State, Zip Code (country)

Sophisticated Knowledge



Anesthesiology is the point at which medicine and technology must precisely converge. And as medicine and technology move forward, the task of maintaining the focus becomes ever more challenging.

At Physio-Control, we believe that our responsibility is to design instruments that meet the demands of both the physical and technical environment. We must communicate as well as measure.

Physio-Control Corporation
Redmond, WA 98073-9706 USA
Toll Free: Outside Washington, 800/426-8047
Inside Washington, 800/562-8071

©1986 Physio-Control Corporation.

**PHYSIO
CONTROL**

ATTENDING ANESTHESIOLOGIST

Position available at Clinical Assistant Professor level for Anesthesiologist—interest in Anesthesia for Ambulatory Surgery helpful. Send curriculum vitae to James E. Cottrell, M.D., Professor and Chairman, Department of Anesthesiology, State University of New York, Health Science Center at Brooklyn, 450 Clarkson Avenue, Box 6, Brooklyn, NY 11203.



State University of New York
**HEALTH SCIENCE CENTER
AT BROOKLYN**

EO/AA Employer, DMC #C-0032.

TRANSPLANTATION ANESTHESIA FELLOWSHIP



University of Pittsburgh
School of Medicine
Department of Anesthesiology

Flexible program includes:

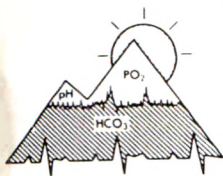
- Hepatic and Cardiac transplantation anesthesia
- Adult and Pediatric clinical experience
- Clinical and laboratory research
- Combined subspecialty rotations

• Several Positions

- 6 months to 1 year
- Beginning January 1987

For Information Contact:

Peter M. Winter, M.D.
Professor and Chairman
Department of Anesthesiology
University of Pittsburgh
1385 Scaife Hall
Pittsburgh, PA 15261
(412) 648-9623



SIXTH ANNUAL CANADIAN WINTER ANAESTHESIA MEETING Quebec City, Que February 22-27, 1987

The Scientific Program includes a wide range of subjects: O.B. Anesthesia, I.C.U., Pediatric Anesthesia, Intraoperative Problems, and Trauma from the E.R. to the O.R.

This Program is approved for A.M.A. Category 1 C.M.E. Credits.

The Scientific Program has been arranged to provide ample time to explore this charming winter setting.

For further information, please write to:

Programme Chairman
Canadian Winter Anaesthesia Meeting
Department of Anaesthesia, Room 2303
The Hospital for Sick Children,
555 University Avenue,
Toronto, Ont. Canada M5G 1X8
or call: (416) 598-7445



CBE STYLE MANUAL Fifth Edition

A guide for Authors, Editors, and Publishers in the Biological Sciences

Widely accepted and recommended as the standard reference for journals and books in the biological sciences

Special features of this newly updated and greatly expanded edition include:

- four new chapters;
- reorganization of the "Manuscript Preparation" section for easier reference;
- new conventions in the chapter on "Style in Special Fields";
- complete revision of the section on "Plant Sciences";
- cross-listing of "Abbreviations and Symbols";
- and much more . . .

CONTENTS: Ethical conduct in authorship and publication • Planning the communication • Writing the article • Prose style for scientific writing • References • Illustrative materials • Editorial review of manuscripts • Application of copyright law • Manuscript into print • Proof correction • Indexing • General style conventions • Style in special fields • Abbreviations and symbols • Word usage • Secondary services for literature searching • Useful references with annotations • Subject index

ISBN: 0-914340-04-2; clothbound; publication date: September 1983; trim size 6 x 9 inches; 324 pages

Regular Price: \$24.00 (10% discount on 10 or more copies delivered to one address)

CBE Member Price: \$21.50 (single copy paid by personal check)

Terms of Sale: All sales final; no returns.

Prepayment required; U.S. currency drawn on a U.S. bank.

Price includes BOOK RATE postage.

For faster delivery--first class, air mail, or UPS available at additional charge (book weight 1 lb 9 oz).

Maryland residents, please add 5% sales tax.

Mail your order with payment to:
COUNCIL OF BIOLOGY EDITORS, INC.
9650 Rockville Pike, Bethesda, MD 20814

Sophisticated Oximetry



The new Physio-Control LIFESTAT® 1600 Pulse Oximeter. Much easier to read and interpret. Temperature compensated sensor. Electrosurgical filtration so that it can maintain accuracy without interference. Portable and battery or line operated so that it can follow the patient to the recovery room.

The Physio-Control LIFESTAT 1600 Pulse Oximeter. A new generation in accuracy, reliability and function. Carefully designed to help you do an even better job.

Physio-Control Corporation
Redmond, WA 98073-9706 USA
Toll Free: Outside Washington, 800/426-8047
Inside Washington, 800/562-8071

©1986 Physio-Control Corporation.

**PHYSIO
CONTRO**

ANESTHESIOLOGIST

Saudi Arabia

Aramco's Dhahran Health Center in Saudi Arabia needs an Anesthesiologist to join a staff of nine Anesthesiologists and five Nurse Anesthetists. The modern 483-bed hospital has been JCAH accredited since 1956 and has all major specialty services. The DHC functions as a referral center for a patient population of approximately 200,000.

American Board Certification and a minimum of two years experience after completion of residency is required.

This overseas assignment offers an excellent opportunity along with a competitive salary and benefit package. For immediate consideration, call **Velma Guy at 1-800-231-7577, ext. 8060 or 713-432-8060**. Or send resume to **Velma Guy, Aramco Services Company, Dept. 06G-024-6, P.O. Box 4530, Houston, Texas 77210-4530**.

ARAMCO

SERVICES COMPANY

CRNA — KENTUCKY

Challenging opportunity available to join the Anesthesiology Department of the largest multi-specialty medical group in Western Kentucky, with 100+ physicians, serving the adjacent 401 bed regional hospital.

Working with a staff of three anesthesiologists and ten CRNAs, this position requires a broad range of anesthesia capability, with regional, OB epidural experience a must. Moderate climate, excellent outdoor activity opportunities, near

Land Between the Lakes

recreational area. Competitive salary and benefit package, with relocation assistance.

Send resume to:

FRANKLIN T. STEVENSON

Assistant Administrator for Clinical Services



TROVER CLINIC

CLINIC DRIVE
MADISONVILLE, KY 42431

502-825-7200



UNIVERSITY OF ROCHESTER MEDICAL CENTER DEPARTMENT OF ANESTHESIOLOGY

ANESTHESIOLOGIST/PHYSIOLOGIST

The Departments of Anesthesiology and Physiology at the University of Rochester are seeking a faculty member to have a joint appointment in the two Departments. Preference will be given to candidates with interest and background in Respiratory Physiology. A Ph.D. in Physiology is desirable but not essential. Board certification in Anesthesiology or its equivalent is required.

Responsibilities will include research, clinical and didactic teaching in Anesthesiology, and didactic teaching in Physiology. Opportunities for collaborative research are abundant. Academic rank and salary will be commensurate with qualifications.

Interested candidates should send curriculum vitae either to:

Ronald A. Gabel, M.D.
Professor and Chairman
Department of Anesthesiology

or to:

Paul Horowicz, Ph.D.
Professor and Chairman
Department of Physiology
University of Rochester Medical Center
601 Elmwood Avenue
Rochester, NY 14642

The University of Rochester is an equal opportunity employer



UNIVERSITY OF ROCHESTER MEDICAL CENTER DEPARTMENT OF ANESTHESIOLOGY

ACADEMIC/ANESTHESIOLOGIST

Expanding University Department of Anesthesiology seeking additional faculty with exemplary qualifications in clinical care, teaching, and research. All major clinical disciplines represented.

Required is a four-year educational continuum or its equivalent, including training in a clinical specialty or in research. Faculty rank and salary commensurate with training and experience. Excellent opportunity for professional development, with facilities for independent or collaborative research.

Send curriculum vitae to:

Ronald A. Gabel, M.D.
Professor and Chairman
Department of Anesthesiology
University of Rochester Medical Center
Rochester, NY 14642

The University of Rochester is an equal opportunity employer

Classified Advertising

PERMANENT POSITION WANTED

CRNA—experienced, wishes busy situation, solo or group, best of remuneration. 1-800-521-6750.

MDAS OR CRNAS: TRANS-AMERICAN ANESTHETISTS, WEST

Temporary or Permanent MDAs, CRNAs, ready to serve you, up-to-date skills, co-operative, licensed, insured professionals caring about you. Call 1-800-762-1258, Box 24432, Colorado Springs, CO 80918, or 303-598-2788 (CO).

ANESTHESIOLOGISTS

Excellent, prequalified individuals available to join your group on a career or temporary basis. For more information please contact: Southwest Anesthesia Services, PO Box 5719, Santa Fe, New Mexico 87502, (505) 983-7371.

ROCKY MTS./SOUTHWEST

We have career and temporary positions available from solo to large group practice in the Rocky Mts. and Southwest. Expenses paid; partnerships usually available. Please contact Southwest Anesthesia Services, PO Box 5719, Santa Fe, NM 87501. (505) 983-7371.

800-FAST GAS: WORLDWIDE ANESTHESIA

Have you got knocks and pings in your Anesthesia Department? Whether it's a short or long-term staff shortage . . . we've got quality MDs and CRNAs to get your program running smoothly! 1-800-327-8427 Worldwide Anesthesia, John Paju, President.

TUTORING FOR WRITTEN AND ORAL BOARD EXAMS:

Individual or small group sessions given in New York City, San Francisco, and Palm Springs. Unique approach to development of test-taking skills, including mock orals. Basic science emphasis. Call 415-321-1117.

CALIFORNIA

Mercy Hospital and Medical Center has an anesthesia residency position at the PGY-3 (CA-2) level available July 1, 1987. Subsequent CA-3 training will be available in OB cardiac and advanced clinical anesthesia. California licensure required. Interested persons may apply to Robert G. Seeman, MD, Acting Director Anesthesia Residency Program, Mercy Hospital and Medical Center, 4077 Fifth Avenue, San Diego, CA 92103.

ANESTHESIOLOGIST

Board certified, board eligible, for group practice in beautiful Catskill, New York. College town, good public schools, hunting, fishing, skiing, close to major cities. Reply to PO Box 819, Norwich, New York 13815.

MICHIGAN

BCBE recent AMG to join group of 4 anesthesiologists supervising CRNAs. Facility with peripheral nerve blocks and invasive monitoring very desirable. Generous salary and benefits first year with possibility of full partnership thereafter. One hour from Detroit on the shores of Lake Huron. Send resumes to Eric J. Robb, MD, Anesthesia Associates of Port Huron, PC, 929 Division Street, PO Box 1219, Port Huron, MI 48060.

ANESTHESIOLOGIST WANTED

for East Central WI city on Lake Mich. Attractive Educational, Cultural and Recreational opportunities. Convenient to Metro Area and Med. School. Chas. Caven Assoc. PO Box 564, Waukesha, WI 53187. (414) 547-7069.

NORTH CAROLINA

Temporary and permanent BE/BC anesthesiologists needed to join fee-for-service group in small community in heart of Blue Ridge Mtns. Salary first year. Send inquiries and CV to Watauga Anesthesia Associates, PA, 301 Birch St, Boone, NC 28607.

ARIZONA

University of Arizona is expanding the Department of Anesthesiology. Academic career potential great. Fellowship or research experience required. Job entails clinical teaching, investigative opportunities. Equal Employment Opportunity/Affirmative Action Employer. Contact Burnell R. Brown, Jr., MD, Anesthesiology Dept., Arizona Health Sciences Center, Tucson, AZ 85724. The closing date for applications is Nov. 30, 1986.

SOUTHWESTERN PA ANESTHESIOLOGIST

BE/BC to join group. All except open heart. Opening immediately. Excellent compensation and future for right person. Response confidential. Pittsburgh area. Submit CV to Box L26, % *Anesthesia and Analgesia*, Desk Editorial, Elsevier Science Publishing Company, 52 Vanderbilt Avenue, New York, NY 10017.

ARIZONA

University of Arizona seeking academically oriented obstetric anesthesiologist to lead new program. Opportunities for research, clinical teaching, and career expansion. Equal Employment Opportunity/Affirmative Action Employer. Contact Burnell R. Brown Jr., MD, Anesthesiology Dept., Arizona Health Sciences Center, Tucson, AZ 85724. The closing date for applications is Nov. 30, 1986.

NORTH CAROLINA

Anesthesiologist BC/BE sought for MD-CRNA team at progressive 250-bed hospital in western piedmont mid-sized town. Submit CV to Box AA1, % *Anesthesia and Analgesia*, Elsevier Science Publishing Co., 52 Vanderbilt Avenue, New York, NY 10017.

NEW ENGLAND

Immediate opening for BC/BE MDA in coastal New England town. No neuro or open heart. Income guarantee. NAMA, PO Box 24, Carlisle, MA 01741. (617) 369-5980.

ANESTHESIOLOGIST SEEKING CHAIRMAN

for established anesthesia department in 400-bed suburban Chicago, Illinois hospital. All surgical specialties represented, including open heart. Must be board certified with 7 yr minimum in academic environment. Excellent financial arrangements. Send CV to CSS Associates, 6819 Winston Drive, Tinley Park, Illinois 60477.

CLASSIFIED ADS

Anesthesia and Analgesia makes available classified advertising space for those interested in obtaining positions, or wishing to announce meetings, postgraduate courses, or other events. Display space (minimum 1/4 page) is also available through Pharmaceutical Med. a, Inc. Rates for classified advertising: **\$1.00 per word, minimum twenty words. Additional fee of \$12.00 for box number ads.** Copy deadline 7 weeks prior to publication, e.g., for the March issue, copy should be received by the 1st of January. Full payment or institutional purchase order must accompany the copy for each ad. Ads received without a check or purchase order will be returned. Ad copy, subject to acceptance by publisher, should be typed double-spaced and mailed in duplicate to:
Anesthesia and Analgesia
Desk Editorial
Classified Ads
Elsevier Science Publishing Co, Inc,
52 Vanderbilt Avenue, New York, NY 10017.
Make checks payable to Elsevier Science Publishing Co, Inc.

TENNESSEE, NASHVILLE-FELLOWSHIPS

Vanderbilt University Medical Center offers fellowships of either 6 months or 1 year duration in pain control, neuroanesthesia, pediatric, obstetric, cardiovascular, and peripheral vascular anesthesia. Positions available to commence February 1, 1987. Active clinical service in all subspecialties provide excellent opportunities for clinical experience and teaching. Interested candidates should send curriculum vitae to Margaret Wood, MD, Department of Anesthesia, Vanderbilt University Medical Center, Nashville, TN 37232.

CENTRAL MARYLAND

Opportunity for BC/BE anesthesiologists beginning January 1987. Good location. Corporate benefits. Minimal call. Send CV to Box AA2, % *Anesthesia and Analgesia*, Elsevier Science Publishing Co., 52 Vanderbilt Avenue, New York, NY 10017.

ALABAMA

Several immediate openings. We are consultants for anesthesiologists and charge no placement fees. Send reply in confidence to Medical Management, Inc., PO Drawer 7308, Montgomery, AL 36107.

NEW YORK

Anesthesiologist for 72-bed community hospital with 1500 surgical procedures per year, available due to death of department chairman. Potential of becoming department chairman, must be board certified or have successfully passed Part I. Located 20 miles west of downtown Rochester in educational community, outstanding recreational and social opportunities. Please send CV to Chief Executive Officer, Lakeside Memorial Hospital, 156 West Avenue, Brockport, NY 14420.

PRIVATE TUTORING AVAILABLE FOR WRITTEN AND ORAL BOARD EXAMS

Send name, address, and phone to Box ANA 5-84-E, % *Anesthesia and Analgesia*, Desk Editorial, Elsevier Science Publishing Co., Inc., 52 Vanderbilt Avenue, New York, NY 10017.

NEW YORK: PEDIATRIC ANESTHESIOLOGIST

Expanding division of pediatric anesthesia, Department of Anesthesiology, Columbia University College of Physicians and Surgeons, is seeking individuals at the Assistant Professor/Associate Professor level with training in anesthesia and pediatrics. Division responsibilities are in the operating room and intensive care unit. Applicants should possess board certification or eligibility, excellent clinical and teaching skills as well as research interests. Interested individuals should reply to: Peter Rothstein, MD, Director, Division of Pediatric Anesthesia, Box 62, Babies Hospital, 622 West 168th Street, New York, NY 10032. Columbia University takes affirmative action to ensure equal opportunity.

CALIFORNIA: ANESTHESIOLOGIST

Full-time faculty position at the Associate/Full Professor level in expanding, young department with emphasis on teaching and research. Complete clinical services in one hospital. Prerequisites include board certified; meet California license requirements; clinical expertise in neuro, pain and/or pediatrics; demonstrated ability as a research scientist and ability to write scholarly articles. Send curriculum vitae, bibliography and names of five references to John H. Eisele, JR, MD, Anesthesiology Department, University of California, Davis, Medical Center, 2315 Stockton Blvd., Sacramento, CA 95817. Position open until filled but not later than January 31, 1987. We are an Equal Opportunity/Affirmative Action Employer.

ANESTHESIOLOGIST

Full time faculty position available for board eligible Anesthesiologist with fellowship training in a subspecialty area (obstetrical anesthesia, cardiac anesthesia, or neuroanesthesia). Faculty rank will be commensurate with experience. Duties include patient care, teaching and research. Send CV to James R. Harp, MD, Professor and Chairman, Department of Anesthesiology, Temple University School of Medicine, Broad and Ontario Streets, Philadelphia, PA 19140. An equal opportunity/affirmative action employer.

SPECIALTY YEAR, ANESTHESIOLOGY RESIDENCY

Positions in the third year of clinical anesthesia training (CA-3) will be available starting July 1987. The year can be made up of blocks of 3-12 months in Cardiac Anesthesia, Critical Care Medicine, Neuroanesthesia, and Pain Treatment. For application form, call 716-275-2141 or write to Mrs. Connie Slade, Department of Anesthesiology, University of Rochester Medical Center, 601 Elmwood Avenue, Rochester, NY 14642.

ANESTHESIOLOGISTS

Expansion of ambulatory surgery center in progress; opening July/August 1987. Approximately 8000 cases/year. Limited call. Previous experience or pediatric fellowship preferred. Excellent cultural, educational, and recreational resources. Liberal salary and fringe benefits. Send resume to CNY Anesthesia Group, PC, 736 Irving Avenue, Syracuse, New York 13210.

NORTH CAROLINA

Anesthesiologist (BE/BC) wanted for thriving anesthesia practice in eastern North Carolina coastal plains city of 25,000 to join group of one MDA and three CRNAs in 200-bed hospital. All surgical subspecialties except Neuro and OH. Send CV to Box X60, % *Anesthesia and Analgesia*, Elsevier Science Publishing Company, Desk Editorial, 52 Vanderbilt Avenue, New York, NY 10017.

ABLE, AFFABLE, AND AVAILABLE

(After April 1, 1987) Anesthesiologist, 33, AMG, University-trained, now looking for position. Colorado, California preferred. Reply to Box AA3, % *Anesthesia and Analgesia*, Elsevier Science Publishing Co., 52 Vanderbilt Avenue, New York, NY 10017.

ORAL BOARD REVIEW

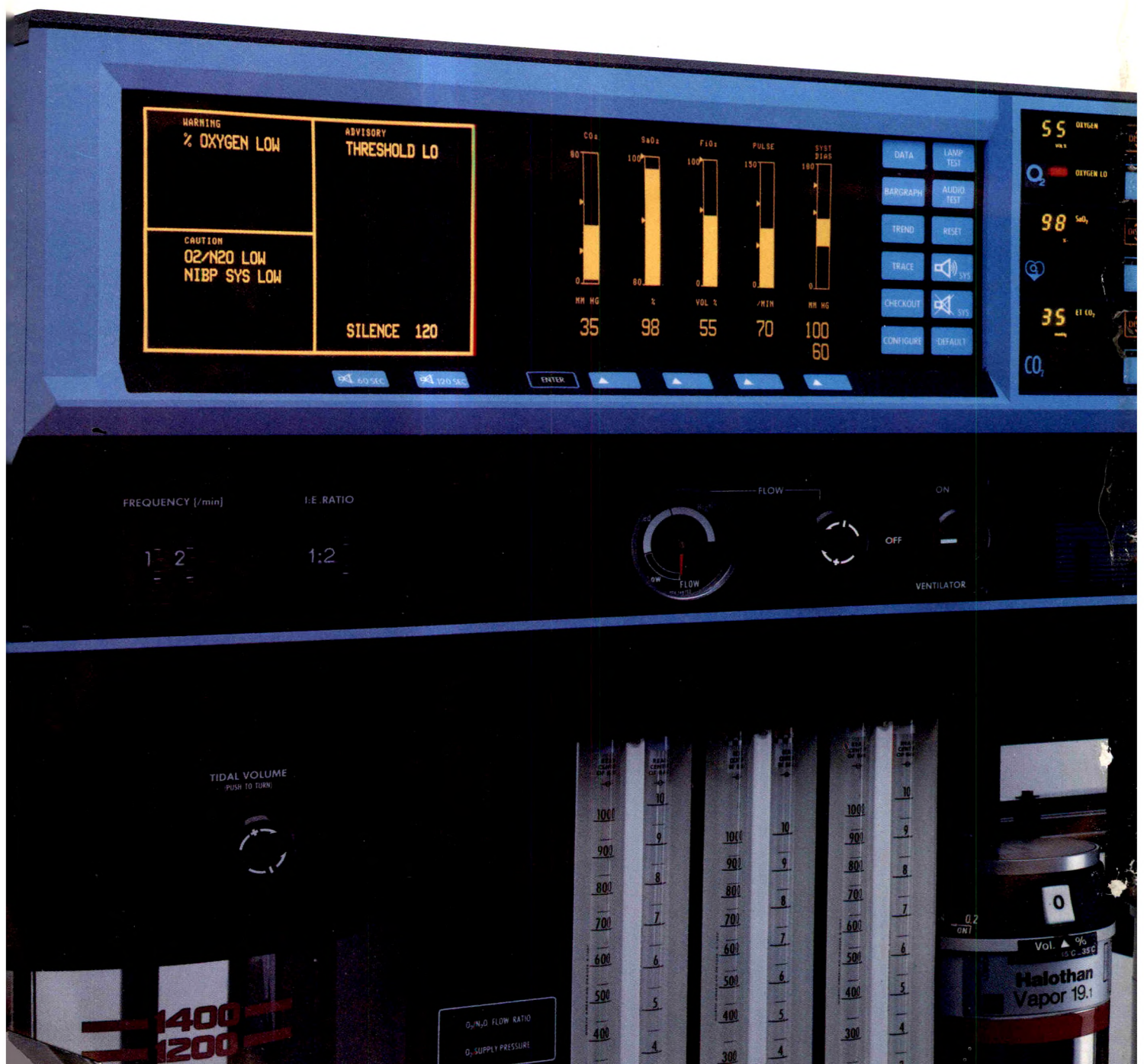
Practice exams with critique. Intensive weekend course in Tampa, FL. Feb. 13-15. Two instructors. Limited class size. Reply: 2656 Gunckel Bl., Toledo, OH 43606, or (419) 475-9641.

INDEX TO ADVERTISERS

Aramco	
<i>Employment Opportunities</i>	A18
Bivona, Inc.	
PVC Fome-Cuf	A14
Bristol Laboratories	
<i>Stadol</i>	Cover 4
Classified Advertising	A19-A20
The Hospital for Sick Children	
<i>Continuing Education</i>	A17
Janssen Pharmaceutica	
<i>Sufenta</i>	A6-7
North American Drager	
<i>Narkomed 3</i>	A22-Cover 3
Organon Pharmaceuticals	
<i>Norcuron</i>	A9-A12
<i>Pavulon</i>	Cover 2
Physio-Control Corporation	
<i>Lifestat 1600</i>	A16-A17
Siemens Elema Ventilator Systems	
<i>Servo Gas Monitor</i>	A13
State University of New York	
<i>Employment Opportunities</i>	A16
Trover Clinic	
<i>Employment Opportunities</i>	A18
University of Pittsburgh	
<i>Employment Opportunities</i>	A16
University of Rochester	
<i>Employment Opportunities</i>	A18

Advertising Office: Pharmaceutical Media, Inc., 130 Madison Avenue, 6th Floor, New York 10016. Telephone: (212) 685-5010

Narkomed unparalleled **3...** **power** **and** **performance**



Narkomed 3 is a new system combining the most reliable basic anesthesia delivery instrument with the most powerful and unique information and monitoring capability available anywhere. From the instant you energize the system... with a single switch... your control of Narkomed 3 can be classified as a breakthrough experience.

What's new about the patient-data displays?

Everything you see on this unique integrated and prioritized data-display screen is new. This is a sampling.

- Central Alarm Display, a tabulation in Warning, Caution, and Advisory format.
- Bargraph display of five important measurements for instant qualitative assessment.
- Central display for quantitative anesthesia documentation, with optional hardcopy presentation.
- Waveform display of respiratory measurements.
- Trending display of all anesthesia monitoring system measurements.

What is monitored by the Narkomed 3?

Six integrated monitors are available, from a total of eight, for display of patient-status data. Depending upon your choice, the information presented comprises...

- | | |
|--|--|
| <input type="checkbox"/> Oxygen Concentration | <input type="checkbox"/> Breathing Pressures |
| <input type="checkbox"/> Pulse Oximetry | <input type="checkbox"/> Carbon Dioxide |
| <input type="checkbox"/> Respiratory Volumes | <input type="checkbox"/> Blood Pressures |
| <input type="checkbox"/> Anesthesia Concentrations | <input type="checkbox"/> Temperatures |

The first two monitoring sources are standard. The other six monitors are optional. With an optional interface, certain other external monitors can be added.

Why hasn't there been a system like this before?

Because the variety of monitors now available were introduced, by many different makers, over a period of more than ten years. Often, the information they provided was not used because it was not controlled, integrated, or prioritized. Now, the unique Narkomed 3 puts you in full control of the system, with less effort. Experience it now. Contact your NAD Dealer, or call us directly.



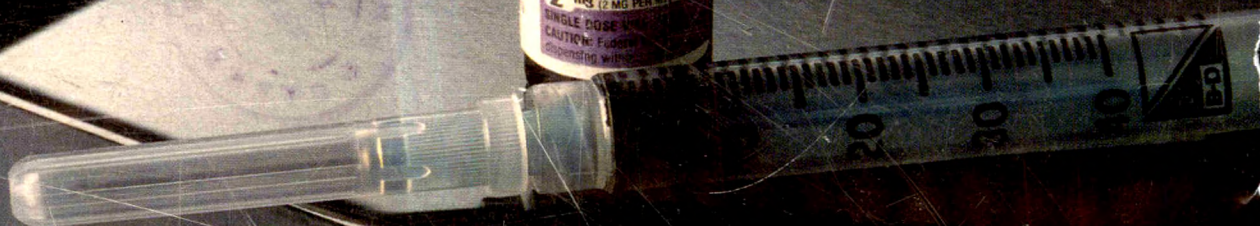
**NORTH
AMERICAN
DRÄGER**

148B Quarry Road
Telford, Pennsylvania 18969
(215) 723-9824
or 248-0834
TWX 510-661-6148
NOAMDRAGER TEL





INSTEAD.



BRISTOL®

© 1985 Bristol Laboratories
Division of Bristol-Myers Company
Syracuse, New York 13221-4755